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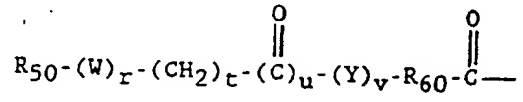

XL_{2b}

(57) Abstract

The present invention provides novel renin-inhibiting peptides of the formula X-A_6-B_7-C_8-D_9-E_{10}-F_{11}-G_{12}-H_{13}-I_{14}-Z, containing aryl acid derived moieties of the formula XL_{2b} which are substituted for Phe^8-His^9, X and Z are terminal groups, and the remaining variables are absent or are amino acid residues. Such inhibitors are useful for the diagnosis and control of renin-dependent hypertension and other related diseases.

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RENIN INHIBITING PEPTIDES WITH NONPEPTIDE LINKAGES

DESCRIPTION

BACKGROUND OF THE INVENTION

The present invention provides novel compounds. More particularly, the present invention provides novel renin-inhibiting peptide analogs with nonpeptide linkages. Most particularly, the present invention provides renin-inhibitory compounds which contain modifications of the Phe^8-His^9 (angiotensinogen numbering) positions. The modifications involve substitution of nonproteinogenic (non α-amino acid) moieties for the usual α-amino acid residues. Specifically, aryl acid derived moieties are substituted for Phe^8-His^9. The renin inhibitors provided herein are useful for the diagnosis and control of renin-dependent hypertension and other related diseases.

Renin is an endopeptidase which specifically cleaves a particular peptide bond of its substrate (angiotensinogen), of which the N-terminal sequence in equine substrate is for example:

Renin
↓
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Leu-Val-Tyr-Ser- IA
1 2 3 4 5 6 7 8 9 10 11 12 13 14

as found by L.T. Skeggs et al, J. Exper. Med. 106, 439 (1957). Human renin substrate has a different sequence as recently discovered by D.A. Tewkesbury et al, Biochem. Biophys. Res. Comm. 99, 1311 (1981). It may be represented as follows:

Renin
↓
-Val-Ile-His-
11 12 13 IB

and having the sequence to the left of the arrow (↓) being as designated in formula IA above.

Renin cleaves angiotensinogen to produce angiotensin I, which is converted to the potent pressor angiotensin II. A number of angiotensin I converting enzyme inhibitors are known to be useful in the treatment of hypertension. Inhibitors of renin are also useful in the treatment of hypertension.

A number f renin-inhibitory peptides have been disclosed. Thus, U.S. Patent 4,424,207; European published applications 45,665; 104,041;

and 156,322; and U.S. patent application, Serial No. 825,250, filed 3 February 1986; disclose certain peptides with the dipeptide at the 10,11-position containing an isostere bond. A number of statine derivatives stated to be renin inhibitors have been disclosed, see, e.g., European published applications 77,028; 81,783; 114,993; 156,319; and 156,321; and U.S. patents 4,478,826; 4,470,971; 4,479,941; and 4,485,099. Terminal disulfide cycles have also been disclosed in renin inhibiting peptides; see, e.g., U.S. patents 4,477,440 and 4,477,441. Aromatic and aliphatic amino acid residues at the 10,11 position of the renin substrate are disclosed in U.S. patents 4,478,827 and 4,455,303. C-terminal amide cycles are disclosed in U.S. patent 4,485,099 and European published applications 156,320 and 156,318. Certain tetrapeptides are disclosed in European publications 111,266 and 77,027. Further, European published application No. 118,223 discloses certain renin inhibiting peptide analogs where the 10-11 peptide link is replaced by a one to four atom carbon or carbon-nitrogen link. Additionally, Holladay et al., in "Synthesis of Hydroxyethylene and Ketomethylene Dipeptide Isosteres", Tetrahedron Letters, Vol. 24, No. 41, pp. 4401-4404, 1983 disclose various intermediates in a process to prepare stereo-directed "ketomethylene" and "hydroxyethylene" dipeptide isosteric functional groups disclosed in the above noted U.S. Patent No. 4,424,207. Evans, et al., J. Org. Chem., 50, 4615 (1985) discloses the synthesis of Hydroxyethylene Dipeptide Isosteres. See also, published European patent application 163,237, which discloses certain renin inhibiting peptides.

Additionally, published European Applications 45,161 and 53,017 disclose amide derivatives useful as inhibitors of angiotensin converting enzymes.

Certain dipeptide and tripeptides are disclosed in U.S. patents 4,514,332; 4,510,085; and 4,548,926 as well as in European published applications 128,762; 152,255; and 181,110. Pepstatin derived renin inhibitors have been disclosed in U.S. patent 4,481,192. Retroinverso bond modifications at positions 10-11 have been disclosed in U.S. patent 4,560,505 and in European published applications 127,234 and 127,235. Derivatives of isosteric bond replacements at positions 10-11 have been disclosed in European published applications 143,746 and 144,290; and PCT application, Serial No. 000,291, filed 13 February 1987. Isosteric bond modifications at positions 11-12 and 12-13 have

been disclosed in European published application 179,352. Certain peptides containing 2-substituted statine analogues have been disclosed in European published application 157,409. Certain peptides containing 3-aminodeoxystatine have been disclosed in European published application 161,588. Certain peptides containing 1-amino-2-hydroxybutane derivatives at positions 10-11 have been disclosed in European published application 172,346. Certain peptides containing 1-amino-2-hydroxypropane derivatives at positions 10-11 have been disclosed in European published application 172,347. Certain peptides containing N-terminal amide cycles have been disclosed in U.S. patent application, Serial No. 844,716, filed 27 March 1986. Certain peptides containing dihalostatine have been disclosed in PCT application, Serial No. 000,713, filed 7 April 1986. Certain peptides containing C-terminus truncated epoxy or azido or cyano groups or containing a position 10-11 diol and a position 11-12 retro bond have been disclosed in U.S. patent application, Serial No. 945,340, filed 22 December 1986.

European published applications 156,322; 114,993; and 118,223; and PCT patent application, Serial No. 002,227, filed 21 November 1986; U.S. patent application, Serial No. 825,250, filed 3 February 1986; PCT application, Serial No. 000,291, filed 13 February 1987; and U.S. patent application, Serial No. 844,716, filed 27 March 1986; disclose hydroxamic acids or esters at the C-terminus.

E.P. 189,203 discloses new N-dihydroxyalkyl peptide derivatives which are useful as inhibitors of renin for treating hypertension.

E.P. 184,855 discloses new hydroxy substituted-statine peptide derivatives which are useful as inhibitors of renin for treating hypertension.

Derivatives of isosteric bond replacements at positions 10-11 as dihydroxy ethylene isosteres have been disclosed in PCT application, Serial No. 000,291, filed 13 February 1987.

The following references disclose additional substituents at the 10, 11-position: A. Spaltenstein, P. Carpino, F. Miyake and P.B. Hyskins, Tetrahedron Letters, 27:2095 (1986); D.H. Rich and M.S. Bernatowicz, J. Med. Chem., 25:791 (1982); Roger, J. Med. Chem., 28:1062 (1985); D.M. Glick et al., Biochemistry, 21:3746 (1982); D.H. Rich, Biochemistry, 24:3165 (1985); R.L. Johnson, J. Med. Chem., 25:605 (1982); R.L. Johnson and K. Verschovor, J. Med. Chem., 26:1457 (1983); R.L. Johnson, J. Med. Chem., 27:1351 (1984); P.A. Bartlett and W.B.

Kezer et al., J. Am. Chem. Soc., 106:4282 (1984); Peptides: Synthesis, Structure and Function (V.J. Hruby; D.H. Rich, eds.) Proc. 8th American Peptide Sym., Pierce Chemical Company, Rockford, Ill., pp. 511-20; 587-590 (1983).

INFORMATION DISCLOSURE

PCT application, Serial No. 002,227, filed 21 October 1986, claiming priority date of U.S. application, Serial No. 798,459, filed 15 November 1985, discloses novel renin inhibiting polypeptide analogs containing S-aryl-D- or L- or DL-cysteinyl,3-(arylthio) lactic acid or 3-(arylthio) alkyl moieties.

European published applications 045 665, 118 223, and 104 041 disclose isosteric replacements of the "reduced" ($\psi[CH_2NH]$) kind at one or both of the Pro-Phe or Phe-His links in compounds of the formula X-Y-Pro^7-Phe^8-His^9-$A^{10,11}$-B-Z-W.

European published application 206 090 discloses hydroxyethylene-type isosteres to the left of the transition state insert of renin inhibitors.

SUMMARY OF THE INVENTION

The present invention particularly provides:

A renin inhibitory peptide having a non-cleavable transition state insert corresponding to the 10,11-position of a renin substrate (angiotensinogen) and having a moiety of the formula XL_{2b} in place of amino acid residues normally found at the 8,9- position of the renin substrate;

wherein R_{50} is

(a) aryl,

(b) -Het,

(c) (C_3-C_7)cycloalkyl,

(d) $R_{51}NHCH(R_{52})(CO)$-, or

(e) $R_{51}CH(R_{52})NH(CO)$-;

provided that R_{50} is the substituent in (d) only when r, t, and u are all zero;

provided that R_{50} is the substituent in (e) only when r, t, u and v are all zero;

wherein R_{51} is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) R_5-O-CH_2-C(O)-,

(d) R_5-CH_2-O-C(O)-,

(e) R_5-O-C(O),

(f) R_5-$(CH_2)_n$-C(O)-,

(g) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(h) R_5-SO_2-$(CH_2)_q$-C(O)-,

(i) R_5-SO_2-$(CH_2)_q$-O-C(O)-, or

(j) R_6-$(CH_2)_i$-C(O)-;

wherein R_{52} is

(a) aryl,

(b) -$(C_1$-$C_4)$alkylaryl,

(c) -$(C_2$-$C_4)$alkenylaryl,

(d) -$(C_1$-$C_4)$alkyl-$(C_5$-$C_7)$cycloalkyl,

(e) -S-aryl,

(f) -S-$(C_5$-$C_7)$cycloalkyl, or

(g) -Het;

wherein R_{60} is

(a) aryl, or

(b) -Het;

provided that R_{60} is substituted at the ortho or meta position;

wherein W is

(a) -S-,

(b) -O-, or

(c) -NH-;

wherein i is zero to five, inclusive;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein q is one to five, inclusive;

wherein Y is

(a) -S-,

(b) -O-, or

(c) -NH-;

wherein r is zero or 1;

wherein t is zero to 3 inclusive;

wherein u is zero or 1;

wherein v is zero or 1;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

U.S. patent application, Serial No. 904,149, filed 5 September 1986; U.S. patent application, Serial No. 844,716, filed 27 March 1986; PCT application, Serial No. 000,713, filed 7 April 1986; U.S. patent application, Serial No. 945,340, filed 22 December 1986; and U.S. patent application, Serial No. 825,250, filed 3 February 1986; and

A. Spaltenstein, P. Carpino, F. Miyake and P.B. Hyskins, Tetrahedron Letters, 27:2095 (1986); D.H. Rich and M.S. Bernatowicz, J. Med. Chem., 25:791 (1982); Roger, J. Med. Chem., 28:1062 (1985); D.M. Glick et al., Biochemistry, 21:3746 (1982); D.H. Rich, Biochemistry, 24:3165 (1985); R.L. Johnson, J. Med. Chem., 25:605 (1982); R.L. Johnson and K. Verschovor, J. Med. Chem., 26:1457 (1983); R.L. Johnson, J. Med. Chem., 27:1351 (1984); P.A. Bartlett et al., J. Am. Chem. Soc., 106:4282 (1984); and Peptides: Synthesis, Structure and Function (V.J. Hruby; D.H. Rich, eds.) Proc. 8th American Peptide Sym., Pierce Chemical Company, Rockford, Ill., pp. 511-20; 587-590 (1983).

As is apparent to those of ordinary skill in the art, the renin inhibitory peptides of the present invention can occur in several isomeric forms, depending on the configuration around the asymmetric carbon atoms. All such isomeric forms are included within the scope of the present invention. Preferably, the stereochemistry of the other amino acids corresponds to that of the naturally-occurring amino acids.

Renin inhibitory peptides commonly have protecting groups at the N-terminus and the C-terminus. These protecting groups are known in the polypeptide art. Examples of these protecting groups are given below. Any of these protecting groups are suitable for the renin inhibitory peptides of the present invention.

Furthermore, the non α-amino acid moieties of the formula XL_{2b} of the present invention may occur at the N-terminus of the renin inhibitory peptide and, as such, will, when coupled with a suitable protecting group, assume the ending position.

These compounds are shown in relation to the human renin substrate as follows:

6	7	8	9	10	11	12	13	
-His	Pro	Phe	His	Leu	Val	Ile	His-	
X	A_6	B_7	C_8	D_9	E_{10}	F_{11}	G_{12}	H_{13}	I_{14}	Z,

The present invention provides peptide inhibitors of renin which contain at least one non α-amino acid moiety and have transition state inserts.

Examples of pharmaceutically acceptable acid addition salts include: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix (C_i-C_j) indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus (C_1-C_4)alkyl refers to alkyl of one to 4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl, and isomeric forms thereof. C_4-C_7cyclic amino indicates a monocyclic group containing one nitrogen and 4 to 7 carbon atoms.

Examples of (C_3-C_{10})cycloalkyl which include alkyl-substituted cycloalkyl containing a total of up to 10 total carbon atoms, are cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3-diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and isomeric forms thereof.

Examples of aryl include phenyl, naphthyl, (o-, m-, p-)tolyl, (o-, m-, p-)ethylphenyl, 2-ethyl-tolyl, 4-ethyl-o-tolyl, 5-ethyl-m-tolyl, (o-, m-, or p-)propylphenyl, 2-propyl-(o-, m-, or p-)tolyl, 4-isopropyl-2,6-xylyl, 3-propyl-4-ethylphenyl, (2,3,4- 2,3,6-, or 2,4,5-)-trimethylphenyl, (o-, m-, or p-)fluorophenyl, (o-, m-, or p-trifluoromethyl)phenyl, 4-fluoro-2,5-xylyl, (2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)difluorophenyl, (o-, m-, or p-)chlorophenyl, 2-chloro-p-tolyl, (3-, 4-, 5- or 6-)chloro-o-tolyl, 4-chloro-2-propylphenyl, 2-isopropyl-4-chlorophenyl, 4-chloro-3-fluorophenyl, (3- or 4-)chloro-2-fluorophenyl, (o-, m-, or p-)trifluoro-methylphenyl, (o-, m-, or p-)ethoxyphenyl, (4- or 5-)chloro-2-methoxy-phenyl, and 2,4-dichloro(5- or 6-)methylphenyl, and the like.

Examples of -Het include: 2-, 3-, or 4-pyridyl, imidazolyl,

indolyl, N^{in}-formyl-indolyl. N^{in}-C_1-C_5alkyl-C(0)-indolyl, [1,2,4]-triazolyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-thienyl, piperidinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyrazinyl, piperazinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, and benzothienyl. Each of these moieties may be substituted as noted above.

As would be generally recognized by those skilled in the art of organic chemistry, a heterocycle as defined herein for -Het would not be bonded through oxygen or sulfur or through nitrogen which is within a ring and part of a double bond.

Halo is halogen (fluoro. chloro, bromo, or iodo) or trifluoromethyl.

Examples of pharmaceutically acceptable cations include: pharmacologically acceptable metal cations, ammonium, amine cations, or quaternary ammonium cations. Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are also within the scope of this invention. Pharmacologically acceptable amine cations are those derived from primary, secondary, or tertiary amines.

The novel peptides herein contain both natural and synthetic amino acid residues. These residues are depicted using standard amino acid abbreviations (see, e.g., Eur. J. Biochem., 138, 9 (1984)) unless otherwise indicated.

In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The renin inhibitors of this invention are useful for treating any medical condition for which it is beneficial to reduce the levels of active circulating renin. Examples of such conditions include renin-associated hypertension and hyperaldosteronism, hypertension, hypertension under treatment with another antihypertensive and/or a diuretic agent, congestive heart failure, angina, and post-myocardial infarction. The renin-angiotension system may play a role in maintenance of

intracellular homeostasis: see Clinical and Experimental Hypertension, 86, 1739-1742 (1984) at page 1740 under Discussion. The compounds will also be useful as molecular probes for the diagnosis and study of the physiology of blood pressure regulation or other physiological functions.

Inhibitors containing these "non-natural" residues are potent inhibitors of human plasma renin. The novel non-peptidic nature of these inhibitors is expected to alter their absorption, distribution, metabolism, and elimination. The new residues make the inhibitor unrecognizable to proteinases, such as chymotrypsin, elastase, or aminopeptidase, which normally would rapidly degrade a substrate-based peptidic inhibitor. These compounds represent a significant step toward non-substrate based renin inhibitors.

Further, the renin inhibitors of this invention may be useful in the treatment of cerebrovascular disorders and disorders of intracellular homeotasis. The possible role of the renin-angiotensin system in the maintenance of intracellular homeostasis is disclosed in Clinical and Experimental Hypertension, 86:1739-1742.(1984). Additionally, the renin inhibitors of this invention potentiate the antithrombotic activity of a thromboxane antagonist (U.S. patent 4,558,037). The antihypertensive effect of the renin inhibitors of this invention are potentiated by combination with a thromboxane synthetase inhibitor.

The compounds of the present invention are preferably orally administered to humans to effect renin inhibition for the purpose of favorably affecting blood pressure. For this purpose, the compounds are administered from 0.1 mg to 1000 mg per kg per dose, administered from 1 to 4 times daily. The compounds of the present invention are preferably orally administered in the form of pharmacologically acceptable acid addition salts. Preferred pharmacologically acceptable salts for oral administration include the citrate and aspartate salts, although any pharmacologically acceptable salt is useful in this invention, including those listed above. These salts may be in hydrated or solvated form.

Other routes of administration include parenteral, by inhalation spray, transdermally or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used her in includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or

infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example as a sterile injectable aqueous r oleagenous suspension. This suspension may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectibles.

Equivalent dosages for such other routes of administration are thus employed. The exact dose depends on the age, weight, and condition of the patient and on the frequency and route of administration. Such variations are within the skill of the practitioner or can readily be determined.

The compounds of the present invention may be in the form of pharmaceutically acceptable salts both those which can be produced from the free bases by methods well known in the art and those with which acids have pharmacologically acceptable conjugate bases.

Conventional forms and means for administering renin-inhibiting compounds may be employed and are described, e.g., in U.S. Patent No. 4,424,207 which is incorporated by reference herein. Likewise, the amounts disclosed in the U.S. Patent No. 4,424,207 are examples applicable to the compounds of the present invention.

The renin-inhibiting compounds of this invention may be administered in combination with other agents used in antihypertensive therapy such as diuretics, α and/or β-adrenergic blocking agents, CNS-acting agents, adrenergic neuron blocking agents, vasodilators, angiotensin I converting enzyme inhibitors, and the like as described, for example, in published European patent application 156 318.

For example, the compounds of this invention can be given in combination with such compounds or salts or other derivative forms thereof as:

Diuretics: acetazolamide; amiloride; bendroflumethiazide; benz-

thiazide; bumetanide; chlorothiazide; chlorthalidone; cyclothiazide; ethacrynic acid; furosemide; hydrochlorothiazide; hydroflumethiazide; indacrinone (racemic mixture, or as either the (+) or (-) enantiomer alone, or a manipulated ratio, e.g., 9:1 of said enantiomers, respectively); metolazone; methyclothiazide; muzolimine; polythiazide; quinethazone; sodium ethacrynate; sodium nitroprusside; spironolactone; ticrynaten; trimaterene; trichlormethiazide;

α-Adrenergic Blocking Agents: dibenamine; phentolamine; phenoxybenzamine; prazosin; tolazoline;

β-Adrenergic Blocking Agents: atenolol; metoprolol; nadolol; propranolol; timolol;

((±)-2-[3-(tert-butylamino)-2-hydroxypropoxy]-2-furananilide) (ancarolol);

(2-acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzofuran HCl)(befunolol);

((±)-1-(isopropylamino)-3-(p-(2-cyclopropylmethoxyethyl)-phenoxy)-2-propranol HCl) (betaxolol);

(1-[(3,4-dimethoxyphenethyl)amino]-3-(m-tolyloxy)-2-propanol HCl)(bevantolol);

(((±)-1-(4-((2-isopropoxyethoxy)methyl)phenoxy)-3-isopropylamino-2-propanol)fumarate) (bisoprolol);

(4-(2-hydroxy-3-[4-(phenoxymethyl)-piperidino]-propoxy)-indole);

(carbazolyl-4-oxy-5,2-(2-methoxyphenoxy)-ethylamino-2-propanol);

(1-((1,1-dimethylethyl)amino)-3-((2-methyl 'H-indol-4-yl)oxy)-2-propanol benzoate) (bopindolol);

(1-(2-exobicyclo[2.2.1]-hept-2-ylphenoxy)-3-[(1-methylethyl)-amino]-2-propanol HCl) (bornaprolol);

(o-[2-hydroxy-3-[(2-indol-3-yl-1,1-dimethylethyl)-amino]propoxy]benzonitrile HCl) (bucindolol);

(α-[(tert.butylamino)methyl]-7-ethyl-2-benzofuranmethanol) (bufur-alol);

(3-[3-acetyl-4-[3-(tert.butylamino)-2-hydroxypropyl]-phenyl]-1,1-diethylurea HCl) (celiprolol);

((±)-2-[2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenoxy]-N-methylacetamide HCl) (cetamolol);

(2-benzimidazolyl-phenyl(2-isopropylaminopropanol));

((±)-3'-acetyl-4'-(2-hydroxy-3-isopropylaminopropoxy)-acetanilide HCl) (diacetolol);

(methyl-4-[2-hydroxy-3-[(1-methylethyl)aminopropoxyl]]-benzene-propanoate HCl) (esmolol);
(erythro-DL-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol);
(1-(tert.butylamino)-3-[0-(2-propynyloxy)phenoxy]-2-propanol (pargolol);
(1-(tert.butylamino)-3-[o-(6-hydrazino-3-pyridazinyl)phenoxy]-2-propanol diHCl) (prizidilol);
((-)-2-hydroxy-5-[(R)-1-hydroxy-2-[(R)-(1-methyl-3-phenylpropyl)-amino]ethyl]benzamide);
(4-hydroxy-9-[2-hydroxy-3-(isopropylamino)-propoxy]-7-methyl-5H-furo[3,2-g][1]-benzopyran-5-one) (iprocrolol);
((±)-5-(tert.butylamino)-2-hydroxypropoxy]-3,4-dihydro-1-(2H)-naphthalenone HCl) (levobunolol);
(4-(2-hydroxy-3-isopropylamino-propoxy)-1,2-benzisothiazole HCl);
(4-[3-(tert.butylamino)-2-hydroxypropoxy]-N-methylisocarbostyril HCl);
((±)-N-2-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]ethyl-N'-isopropylurea) (pafenolol);
(3-[[(2-trifluoroacetamido)ethyl]amino]-1-phenoxypropan-2-ol);
(N-(3-(o-chlorophenoxy)-2-hydroxypropyl)-N'-(4'-chloro-2,3-dihydro-3-oxo-5-pyridazinyl)ethylenediamine);
((±)-N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxyphenyl]-butanamide) (acebutolol);
((±)-4'-[3-(tert-butylamino)-2-hydroxypropoxy]spiro[cyclohexane-1,2'-indan]-1'-one) (spirendolol);
(7-[3-[[2-hydroxy-3-[(2-methylindol-4-yl)oxylpropyl]amino]butyl]thiophylline) (teoprolol);
((±)-1-tert.butylamino-3-(thiochroman-8-yloxy)-2-propanol (tertatolol);
((±)-1-tert.butylamino-3-(2,3-xylyloxy)-2-propanol HCl) (xibenolol);
(8-[3-(tert.butylamino)-2-hydroxypropoxy]-5-methylcoumarin) (bucumolol);
(2-(3-(tert.butylamino)-2-hydroxy-propoxy)benzonitrile HCl) (bunitrolol);
((±)-2'-[3-(tert-butylamino)-2-hydroxypropoxy-5'-fluorobutyrophenone) (butofilolol);
(1-(carbazol-4-yloxy)-3-(isopropylamino)-2-propanol) (carazolol);
(5-(3-tert.butylamino-2-hydroxy)propoxy-3,4-dihydrocarbotyril HCl) (carteolol);

(1-(tert.butylamino)-3-(2,5-dichlorophenoxy)-2-propanol) (clorano-lol);
(1-(inden-4(or 7)-yloxy)-3-(isopropylamino)-2-propanol HCl) (indeno-lol);
(1-isopropylamino-3-[(2-methylindol-4-yl)oxy]-2-propanol) (mepindo-lol);
(1-(4-acetoxy-2,3,5-trimethylphenoxy)-3-isopropylaminopropan-2-ol) (metipranolol);
(1-(isopropylamino)-3-(o-methoxyphenoxy)-3-[(1-methylethyl)amino]-2-propanol) (moprolol);
((1-tert.butylamino)-3-[(5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol) (nadolol);
((S)-1-(2-cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]-2-propanol sulfate (2:1)) (penbutolol);
(4'-[1-hydroxy-2-(amino)ethyl]methanesulfonanilide) (sotalol);
(2-methyl-3-[4-(2-hydroxy-3-tert.butylaminopropoxy)phenyl]-7-methoxy-isoquinolin-1-(2H)-one);
(1-(4-(2-(4-fluorophenyloxy)ethoxy)phenoxy)-3-isopropylamino-2-propanol HCl);
((-)-p-[3-[(3,4-dimethoxyphenethyl)amino]-2-hydroxypropoxy]-β-methyl-cinnamonitrile) (pacrinolol);
((±)-2-(3'-tert.butylamino-2'-hydroxypropylthio)-4-(5'-carbamoyl-2'-thienyl)thiazole HCl) (arotinolol);
((±)-1-[p-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-(isopropylamino)-2-propanol) (cicloprolol);
((±)-1-[(3-chloro-2-methylindol-4-yl)oxy]-3-[(2-phenoxyethyl)amino]-2-propanol) (indopanolol);
((±)-6-[[2-[[3-(p-butoxyphenoxy)-2-hydroxypropyl]amino]ethyl]amino]-1,3-dimethyluracil) (pirepolol);
(4-(cyclohexylamino)-1-(1-naphtholenyloxy)-2-butanol);
(1-phenyl-3-[2-[3-(2-cyanophenoxy)-2-hydroxypropyl]aminoethyl]hydantoin HCl);
(3,4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitroxy-2H-1-benzopyran) (nipradolol);

Angiotensin I Converting Enzyme Inhibitors:

1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline (captopril);
(1-(4-ethoxycarbonyl-2,4(R,R)-dimethylbutanoyl)indoline-2(S)-carboxylic acid);

(2-[2-[(1-(ethoxycarbonyl)-3-phenyl-propyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid);

((S)-1-[2-[(1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid HCl);

(N-cyclopentyl-N-(3-(2,2-dimethyl-1-oxopropyl)thiol-2-methyl-1-oxopropyl)glycine) (pivalopril);

((2R,4R)-2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acid);

(1-(N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl)-cis,syn-octahydroindol-2(S)-carboxylic acid HCl);

((-)-(S)-1-[(S)-3-mercapto-2-methyl-1-oxopropyl]indoline-2-carboxylic acid);

([1(S),4S]-1-[3-(benzoylthio)-2-methyl-1-oxopropyl]-4-phenylthio-L-proline;

(3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1-acetic acid HCl);

(N-(2-benzyl-3-mercaptopropanoyl)-S-ethyl-L-cysteine) and the S-methyl analogue;

(N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline maleate) (enalapril);

N-[1-(S)-carboxy-3-phenylpropyl]-L-alanyl-1-proline;

N^2-[1-(S)-carboxy-3-phenylpropyl]-L-lysyl-L-proline (lysinopril);

Other Antihypertensive Agents: aminophylline; cryptenamine acetates and tannates; deserpidine; meremethoxylline procaine; pargyline; tri-methaphan camsylate; and the like, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly. Coadministration is most readily accomplished by combining the active ingredients into a suitable unit dosage form containing the proper dosages of each. Other methods of coadministration are, of course, possible.

The compounds of the present invention are prepared as depicted in the charts and as described more fully in the Preparations and Examples. In the charts, Ph is used to represent the phenyl ring.

Chart A

The synthesis of the compound of formula A-5 is shown in Chart A.

m-Toluic acid (formula A-1) is photolyzed with bromine to give 3-(bromomethyl) benzoic acid (formula A-2). 3-(Bromomethyl) benzoic acid (formula A-2) is then stirred with two equivalents of sodium thiophenoxide to give m-(phenylthiomethyl)benzoic acid (formula A-3). The acid is coupled to LVA(O-t-BDMS)-Ile-Amp using diethylphosphorylcyanide to give the compound of formula A-4. Removal of the t-butyldimethylsilyl protecting group with tetrabutylammonium fluoride gives the compound of formula A-5.

CHART B

The syntheses of the compounds of formula B-6 and B-7 are shown in Chart B. Chloromethylphenylsulfide (formula B-1) is added to ethyl 2- or 3-hydroxybenzoate (formula B-2) and sodium hydride in hexamethylphosphoramide to give ethyl m-(phenylthiomethyleneoxy)benzoate (formula B-3). The ester is hydrolyzed to give the compound of formula B-4 and the acid is then coupled to LVA(O-t-BDMS)-Ile-Amp to give the compound of formula B-5. The silyl protecting group is removed with tetrabutylammonium fluoride to give the compounds of formula B-6 or B-7.

2 or 3-(Cyclohexylthiomethyleneoxy)benzoyl-LVA-Ile-Amp (the compound of formula B-6 or B-7 wherein the phenylthio group is replaced by a cyclohexylthio group) may be prepared by the same procedures as described above for Chart B. The starting material for this synthesis, chloromethylcyclohexylsulfide, may be prepared as follows:

To cyclohexylmethylsulfide heated at reflux in methylene chloride is added sulfuryl chloride. The reaction mixture is then stirred overnight at room temperature to afford, after concentration in vacuo, chloromethylcyclohexylsulfide.

Other cycloalkyl compounds of the present invention containing the formula XL_{2b} moiety wherein R_{50} is cycloalkyl may be prepared by synthetic procedures similar to that described above.

CHART C

The synthesis of the compound of formula C-5 is detailed in Chart C. Phenoxyacetic acid (formula C-1) is coupled to ethyl anthranilate hydrochloride (formula C-2) using diethylphosphorylcyanide and dimethylaminopyridine to give the compound of formula C-3. The ester is then hydrolyzed to the acid to give the compound of formula C-4 and the acid is coupled with LVA-Ile-Amp using diethylphosphorylcyanide to give the compound of formula C-5.

CHART D

The syntheses of the compounds of formula D-5 and D-6 are outlined in Chart D. Ethyl 2- or 3-aminobenzoate (formula D-2) is coupled with Boc-Phe-OH (formula D-1) using diethylphosphorylcyanide to give the compound of formula D-3. The ester is hydrolyzed to the acid to give the compound of formula D-4 and the acid is coupled to LVA-Ile-Amp using diethylphosphorylcyanide or dicyclohexylcarbodiimide as the coupling agent to give the compound of formula D-5 or D-6.

CHART E

The syntheses of the compounds of formula E-5 and E-6 are given in Chart E. 3-(Phenylthio) propionic acid (formula E-1) is coupled to ethyl 2- or 3-aminobenzoate (formula E-2) to give the compound of formula E-3. The ester is hydrolyzed to the acid to give the compound of formula E-4 and the acid is coupled to LVA-Ile-Amp using diethylphosphorylcyanide to provide the compounds of formula E-5 or E-6.

CHART F

The synthesis of the compound of formula F-5 is shown in Chart F. 2-Aminonicotinic acid (formula F-1) is esterified with methanol and hydrochloric acid and partitioned with methylene chloride and sodium bicarbonate to give methyl 2-aminonicotinate (formula F-2). This is then coupled with Boc-Phe-OH using dicyclohexylcarbodiimide to give the compound of formula F-3. The ester is then hydrolyzed to the acid to give the compound of formula F-4 and the acid is coupled to LVA-Ile-Amp using diethylphosphorylcyanide to give the compound of formula F-5.

CHART G

LVA-Ile-Amp (formula G-8) and LVA(O-t-BDMS)-Ile-Amp (formula G-7) are synthesized in the following manner: Boc-Ile (formula G-1) and 2-(aminomethyl) pyridine (formula G-2) are coupled using dicyclohexylcarbodiimide to give Boc-Ile-Amp (formula G-3). The Boc group is removed with trifluoroacetic acid in methylene chloride and the resulting trifluoroacetate salt is neutralized via extraction from aq. sodium bicarbonate with methylene chloride to give Ile-Amp (formula G-4). Ile-Amp (formula G-4) is coupled with Boc-LVA(O-t-BDMS)-OH (formula G-5), prepared as described in U.S. application Serial No. 825,250, filed 3 February 1986, to give Boc-LVA(O-t-BDMS)-Ile-Amp (formula G-6). The Boc group is removed with trifluoroacetic acid in methylene chloride to give, after neutralization and chromatography, LVA-Ile-Amp (formula G-8) and LVA(O-t-BDMS)-Ile-Amp (formula G-7).

CHART H

The synthesis of the compound of formula H-7 is shown in Chart H. The compound of formula H-1 is coupled with the compound of formula H-2 (wherein X is n-butyl or 2(S) methylbutyl) using dicyclohexylcarbodiimide to give the compound of formula H-3. The Boc group is removed with trifluoroacetic acid in methylene chloride and the resulting trifluoroacetate salt is neutralized via partitioning between methylene chloride and aq. sodium bicarbonate to give the compound of formula H-4. The compound of formula H-4 is coupled with the compound of formula H-5 (see Chart B) using diethylphosphorylcyanide to give the compound of formula H-6. Removal of the t-butyldimethylsilyl protecting group with tetra-n-butylammonium fluoride gives the compound of formula H-7.

CHART I

Methylamine hydrochloride (formula I-2) is coupled with Leuψ[CH(O-t-BDMS)CH_2]Val-OH (formula I-1) using diethylphosphorylcyanide and triethylamine to give the compound of formula I-3. The Boc-protecting group of the compound of formula I-3 is removed with trifluoroacetic acid and methylene chloride and the resulting trifluoroacetate salt is neutralized via partitioning between methylene chloride and aq. sodium bicarbonate to give the compound of formula I-4. The compound of formula I-4 is coupled with the compound of formula I-5 (see Chart B) using diethylphosphorylcyanide to give the compound of formula I-6. The tert-butyldimethylsilyl protecting group of the compound of formula I-6 is removed with tetra-n-butylammonium fluoride to give the compound of formula I-7.

CHART J

3-Hydroxypicolinic acid (formula J-1) is esterified with methanol using concentrated sulfuric acid as the acid catalyst to give methyl 3-hydroxypicolinate (formula J-2). Methyl 3-hydroxypicolinate (formula J-2) is O-alkylated with chloromethylphenylsulfide (formula J-3) using potassium carbonate in dimethylformamide to give the compound of formula J-4. The compound of formula J-4 is hydrolyzed using 1.5 equivalents of 1 N potassium hydroxide in methanol, followed by acidification with 2 N hydrochloric acid to give the compound of formula J-5. The compound of formula J-5 is coupled with Leuψ[CH(OH)-CH_2]Val-Ile-Amp (formula J-6) using diethylphosphorylcyanide to give the compound of formula J-7.

CHART K

The synthesis of the compound of formula K-6 is shown in Chart K. Ethyl salicylate (formula K-2) is O-alkylated with β-bromophenetole (formula K-1) using potassium carbonate in dimethylformamide to give the compound of formula K-3. The ester group of the compound of formula K-3 is then hydrolyzed using 1.5 equivalents of 1 N sodium hydroxide in methanol, followed by acidification with 2 N hydrochloric acid, to give the compound of formula K-4. The compound of formula K-4 is then coupled with Leuψ[CH(OH)CH_2]Val-Ile-Amp (formula K-5) using diethylphosphorylcyanide to give the compound of formula K-6.

CHART L

The synthesis of the compound(s) of formula(s) L-6 and/or L-7 are shown in Chart L. 3,4-Pyridine dicarboxylic anhydride (formula L-1, Aldrich) and D-phenylalanine tert-butyl ester (formula L-2) are stirred in tetrahydrofuran to give the compound(s) of formula(s) L-3 and/or L-4. The compound of formula L-3 and/or L-4 are coupled with 2HCl-LVA-Ile-Amp (L-5) using diethylphosphorylcyanide and triethylamine in methylene chloride and dimethylformamide to give the compound(s) of formula(s) L-6 and/or L-7.

CHART M

The synthesis of the compound(s) of formula(s) M-6 and/or M-7 is outlined in Chart M. 2,3-Pyridine dicarboxylic anhydride (M-1, Aldrich) and D-phenylalanine tert-butyl ester (M-2) are stirred in tetrahydrofuran to give the compound(s) of formula(s) M-3 and/or M-4. The compound(s) of formula M-3 and/or M-4 are coupled with 2HCl-LVA-Ile-Amp (formula M-5) using diethylphosphorylcyanide and triethylamine in methylene chloride and dimethylformamide to give the compound(s) of formula(s) M-6 and/or M-7.

CHART N

The synthesis of the compound of formula N-6 is outlined in Chart N. Ethyl 3-hydroxybenzoate (N-1) is O-alkylated with phenethylbromide (N-2) using potassium hydride in acetonitrile as solvent to give ethyl 3-(phenethyloxy)benzoate (N-3). Ethyl 3-(phenethyloxy)benzoate (N-3) is hydrolyzed using 1 N sodium hydroxide in methanol, followed by acidification with aq. hydrochloric acid, to give 3-(phenethyloxy) benzoic acid (N-4), which in turn is coupled with Leuψ[CH(O-t-BDMS)-CH_2]Val-Ile-Amp using diethylphosphorylcyanide and triethylamine in methylene chloride to give the compound of formula N-5. The t-butyl-dimethylsilyl protecting group of the compound of formula N-5 is

removed using tetra-n-butylammonium fluoride in tetrahydrofuran to give the compound of formula N-6.

CHART O

The synthesis of the compound of formula O-5 is shown in Chart O. Indole-2-carboxylic acid (formula O-1) is coupled to ethyl anthranilate hydrochloride (formula O-2) using dicyclohexylcarbodiimide or diethylphosphorylcyanide and triethylamine to give the compound of formula O-3. The compound of formula O-3 is hydrolyzed to give the compound of formula O-4 and the acid coupled to LVA-Ile-Amp using diethylphosphorylcyanide to give the compound of formula O-5. Synthetic procedures similar to that described above may be used to prepare the compounds of the formula O-5 wherein the indolyl group is replaced by a quinolyl group or a naphthyl group.

CHART P

The synthesis of the compound of formula P-7 is outlined in Chart P. The compound of formula P-1, prepared by the same procedure used to prepare the compound of formula G-5 (see Chart G) which is described in U.S. application, Serial No. 825,250, filed 3 February 1986, is coupled with methylamine hydrochloride of formula P-2 using diethylphosphorylcyanide and triethylamine in the solvent methylene chloride to give the compound of formula P-3. The Boc- protecting group is removed with trifluoracetic acid in methylene chloride to give, after neutralization via methylene chloride-aq. sodium bicarbonate partitioning, the compound of formula P-4. The compound of formula P-4 is coupled with the compound of formula P-5 (see Chart B) using diethylphosphorylcyanide, triethylamine, and methylene chloride to give the compound of formula P-6. The silyl protecting group of the compound of formula P-6 is removed with tetra-n-butylammonium fluoride in tetrahydrofuran to give the compound of formula P-7.

CHART Q

The synthesis of the compound of formula Q-5 is outlined in Chart Q. 2,2-Dimethyl-3-(tert-butyloxycarbonyl)-4R-(2-cyclohexylmethyl)-5R,S-oxazolidine aldehyde (Q-1), prepared as described in PCT application, Serial No. 000,291, filed 13 February 1987, is reacted with isobutylmagnesium chloride to give the protected amino diol of formula Q-2. The isomers are separated via chromatography and the major isomer is deprotected with a solution of acetyl chloride in methanol to give 2S-amino-1-cyclohexyl-3R,4*-dihydroxy-6-methylheptane (Q-3). (Stereo-

chemistry was not determined.) (The HCl salt of compound of formula Q-3 is also disclosed in European published application 189,203.) 2-(Phenylthiomethyleneöxy) benzoic acid (Q-4) (see Chart B) is coupled with the compound of formula Q-3 using diethylphosphorylcyanide, triethylamine, and methylene chloride to give the compound of formula Q-5.

Generally, the renin inhibiting polypeptides may be prepared by solution phase peptide synthetic procedures analogous to those described hereinafter or to those methods known in the art. For example, the carboxylic moiety of N^{α}-t-butyloxycarbonyl (Boc)-substituted amino acid derivatives having suitable side chain protecting groups, if necessary, may be condensed with the amino functionality of a suitably protected amino acid or peptide using a conventional coupling protocol such as dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) or diethylphosphoryl cyanide (DEPC) and triethylamine (Et_3N) in methylene chloride or dimethylformamide. The synthetic procedures used to incorporate the novel moieties herein are analgous to those described, for example, in U.S. patents 4,424,207; 4,470,971; 4,477,440; 4,477,441; 4,478,826; 4,478,827; 4,479,941; and 4,485,099, and copending application Serial No. 753,198, filed 9 July 1985, and copending application Serial No. 825,250, filed 3 February 1986, all of which are expressly incorporated by reference herein. See, also, published European patent applications 45,161; 45,665; 53,017; 77,028; 77,029; 81,783; 104,041; 111,266; 114,993; and 118,223.

Following coupling reaction completion, the N^{α}-Boc moiety may be selectively removed with 45% trifluoroacetic acid with or without 2% anisole (v/v) in methylene chloride. Neutralization of the resultant trifluoroacetate salt may be accomplished with 10% diisopropylethylamine or sodium bicarbonate in methylene chloride.

The incorporation of N^{in}-formyl-Trp into compounds of the present invention is easily accomplished because of the commercial availability of N^{α}-Boc-N^{in}-formyl-Trp-OH. However, the N^{in}-formyl moiety may be introduced into indolyl-substituted amino acid derivatives or related compounds by reaction with HCl-formic acid as reported in the literature, see A. Previero et al, Biochim. Biophys. Acta 147, 453 (1967); Y.C.S. Yang et al, Int. J. Peptide Protein Res. 15, 130 (1980).

The compounds of the present invention may be in either free form or in protected form at one or more of the remaining (not previously

protected) peptide, carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the polypeptide art. Examples of nitrogen and oxygen protection groups are set forth in T.W. Greene, Protecting Groups in Organic Synthesis, Wiley, New York, (1981); J.F.W. McOmie, ed. Protective Groups in Organic Chemistry, Plenum Press (1973); and J. Fuhrhop and G. Benzlin, Organic Synthesis, Verlag Chemie (1983). Included among the nitrogen protective groups are t-butoxycarbonyl (Boc), benzyloxycarbonyl, acetyl, allyl, phthalyl, benzyl, benzoyl, trityl and the like.

The following compounds of the present invention are preferred: 2-(Boc-Phe-amido)benzoyl-LVA-Ile-Amp; 2-(Boc-Phe-amido)nicotinoyl-LVA-Ile-Amp; and 2-(Phenylthiomethyleneoxy)benzoyl-LVA-Ile-Amp.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following Preparations and Examples illustrate the present invention.

In the Preparations and Examples below and throughout this document:

Ac is acetyl;

AMP is 2-(aminomethyl)pyridine;

BOC is t-butoxycarbonyl;

Bz is benzyl;

C is centigrade;

Celite is a filter aid;

Cha is 3-cyclohexylalanine;

CVDA is "Cha-Val diol" where Cha is 3-cyclohexylalanyl, i.e., the moiety of the formula XL_6 wherein R_1 is cyclohexyl and R_{11} is isopropyl and the configuration at each carbon atom with a * is (R);

DCC is dicyclohexylcarbodiimide;

DCU is dicyclohexylurea;

DMF is dimethylformamide;

EtOAc is ethyl acetate;

g is grams;

1-HOBt is 1-hydroxybenzotriazole;

HPLC is high performance liquid chromatography;

I_2 is iodine;

Ile is isoleucine;

IR is infra red spectra;

LVA is Leu ψ [$CH(OH)CH_2$]Val;

LVDA is Leuψ[CH(OH)CH(OH)]Val;

M or mol is mole;

MBA is 2-methylbutylamino (racemic or optically active);

MBAS is 2S-methylbutylamino;

Me is methyl;

min is minute;

ml is milliliter;

MS is mass spectroscopy;

NMR is nuclear magnetic resonance;

NOAl is (1-naphthyloxy)acetyl;

p-TSA salt is para-toluene sulfonic acid salt;

Ph is phenyl;

Phe is phenylalanine;

POA is phenoxyacetyl;

RIP means a compound having the formula H-Pro-His-Phe-His-Phe-Phe-Val-Tyr-Lys-OH.2($CH_3C(O)OH$).XH_2O which is a known renin-inhibiting peptide. Skellysolve B is as defined in the Merck Index, 10th edition;

t-BDMS is t-butyldimethylsilyl;

TFA is trifluoroacetic acid;

THF is tetrahydrofuran;

TLC is thin layer chromatography;

Tos is p-toluenesulfonyl;

Tr is trityl (triphenylmethyl);

2HPA is (±)-(2-hydroxypropyl)amino; and

UV is ultraviolet.

The wedge-shape line indicates a bond which extends above the plane of the paper relative to the plane of the compound thereon.

The dotted line indicates a bond which extends below the plane of the paper relative to the plane of the compound thereon.

The synthesis of statine is disclosed in Evans et al., J. Org. Chem. 47: 3016 (1982). The synthesis of moieties at the $E_{10}F_{11}$ position is disclosed in the following: U.S. patent application, Serial No. 825,250, filed 3 February 1986 (synthesis of LVA); U.S. patent application. Serial No. 000,291, filed 13 February 1987 (synthesis of dihydroxy-LVA; and published European Patent Application

189,203 (synthesis of amino-diol).

Preparation 1 m-(Bromomethyl)benzoic Acid (Formula A-2) Refer to Chart A.

To 0.495 g of m-toluic acid in 20 ml of carbon tetrachloride is added in about five increments 0.205 ml of bromine in carbon tetrachloride. After the addition of each increment, the flask is illuminated with a high intensity light (Sylvania Sun Gun). (When the bromine color disappears, the next increment is added.)

The reaction mixture is partitioned between methylene chloride and hexane to give 0.58 g of the title product.

Physical characteristics are as follows:

M.P.: 127-134°C.

^{1}H-NMR (δ, $CDCl_3$): 4.53, 6.69-8.14.

Anal. Found: C, 43.25; H, 3.09.

Preparation 2 m-(Phenylthiomethyl)benzoic Acid (Formula A-3) Refer to Chart A.

Sodium hydride (60% in oil, 0.0191 g,) is washed twice with hexane. Dimethylformamide (3.5 ml) is added, followed by the dropwise addition of 0.0487 ml of thiophenol. After stirring for 5-10 minutes, the homogeneous solution is cannulated into a solution of 0.0500 g of the title product of Preparation 1 in 2 ml of dimethylformamide. The reaction mixture is stirred at room temperature for 45 min, then at 60°C for 1 h. Dimethylformamide is then removed and the residue is partitioned between diethyl ether, dil. aq. hydrochloric acid, and acidified brine. The organic layers are dried over magnesium sulfate, taken to dryness, and crystallized from diethyl ether-hexane to give 0.0405 g of the title product.

Physical characteristics are as follows:

M.P.: 103.5-104.5°C.

MS: m/z at 244..

^{1}H-NMR (δ, $CDCl_3$): 4.14, 7.15-8.10.

Anal. Found: C, 67.36; H, 4.86.

Preparation 3 m-(Phenylthiomethyl)benzoyl-LVA(o-t-BDMS)-Ile-Amp (Formula A-4) Refer to Chart A.

To 0.0240 g of the title product of Preparation 2, 0.0450 g of LVA(O-t-BDMS)-Ile-Amp, and 2 ml of methylene chloride is added 0.0149 ml of triethylamine, followed by 0.0162 ml of diethylphosphorylcyanide. The reaction is stirred for 1 h and then partitioned between methylene

chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and the residue is chromatographed using 2% methanol-methylene chloride to give 0.0631 g of the title product.

Physical characteristics are as follows:

R_f (4% methanol-methylene chloride): 0.34.

^{1}H-NMR (δ, $CDCl_3$): 0.14, 0.93, 4.12, 4.50, 6.13, 6.23, 7.0-7.75, 8.48.

Example 1 m-(Phenylthiomethyl)benzoyl-LVA-Ile-Amp (Formula A-5) Refer to Chart A.

To 0.0631 g of the title product of Preparation 3 in 1 ml of tetrahydrofuran is added 1 ml of 1 M tetrabutylammonium fluoride (in tetrahydrofuran). After stirring overnight, the solvent is removed in vacuo and the residue is partitioned between methylene chloride, aq. sodium bicarbonate, and brine. The organic layers are filtered through sodium sulfate, concentrated, and chromatographed using 4% methanol-methylene chloride to give 0.0487 g of the title product.

Physical characteristics are as follows:

R_f (4% methanol-methylene chloride): 0.21.

FAB MS: [m + H] at m/z 661.3777.

^{1}H-NMR (δ, $CDCl_3$): 0.73-0.95, 4.08, 4.50, 6.47, 6.70, 7.1-7.65, 8.48.

Anal. Found: C, 68.74; H, 7.90; N, 8.31.

Preparation 4 m-(Phenylthiomethyleneoxy)benzoic acid, ethyl ester (Formula B-3) Refer to Chart B.

To 0.1699 g of ethyl 3-hydroxybenzoate in about 0.5 ml of hexamethylphosphoramide is added 0.045 g of sodium hydride (60% in oil). After stirring for 50 min, 0.1784 g of chloromethylphenylsulfide is added. The reaction is stirred for 35 min and then partitioned between diethyl ether, water, and brine. The organic layers are dried over magnesium sulfate, concentrated, and chromatographed using 5% ethyl acetate-hexane to give 0.2481 g of the title product.

Physical characteristics are as follows:

^{1}H-NMR (δ, $CDCl_3$): 1.28, 4.28, 5.49, 7.05-7.8.

Anal. Found: C, 66.40; H, 5.85.

Preparation 5 m-(Phenylthiomethyleneoxy)benzoic Acid (Formula B-4) Refer to Chart B.

To 0.1052 g of the title product of Preparation 4 in 5 ml of

methanol is added 0.44 ml of 1 N sodium hydroxide. After 30 min, an additional 0.11 ml of 1 N sodium hydroxide is added and after 3 hrs, 0.22 ml of 1 N sodium hydroxide is added. The reaction is stirred overnight, methanol is then removed in vacuo, and the residue is partitioned between diethyl ether, aq. hydrochloric acid, and brine. The organic layers are dried over magnesium sulfate and taken to dryness in vacuo. The residue is crystallized from methylene chloride and hexane to give 0.0879 g of the title product.

Physical characteristics are as follows:

M.P.: 121-122.5°C.

MS: m/z at 260.

^{1}H-NMR (δ, $CDCl_3$): 5.52, 7.1-7.85.

Anal. Found: C, 64.44; H, 4.58.

Preparation 6 m-(Phenylthiomethyleneoxy)benzoyl-LVA(O-t-BDMS)-Ile-Amp (Formula B-5) Refer to Chart B.

To 0.0298 g of the title product of Preparation 5, 0.0523 g of LVA(O-t-BDMS)-lLe-Amp, and 7 ml of methylene chloride is added 0.0173 ml of triethylamine, followed by 0.0188 ml of diethylphosphorylcyanide. After stirring for 1.75 hr. the reaction is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and chromatographed using 2% methanol-methylene chloride (ammonium hydroxide sat'd) to give 0.0694 g of the title product.

Example 2 m-(Phenylthiomethyleneoxy)benzoyl-LVA-lle-Amp (Formula B-6) Refer to Chart B.

To 0.0694 g of the title product of Preparation 6 in 0.5 ml of tetrahydrofuran is added 0.5 ml of 1 M tetrabutylammonium fluoride (in tetrahydrofuran). After stirring overnight, tetrahydrofuran is removed in vacuo and the residue is partitioned between methylene chloride and water. The organic layers are filtered through sodium sulfate, concentrated, and chromatographed using 2% methanol-methylene chloride (ammonium hydroxide sat'd) to give 0.061 g of the title product.

Physical characteristics are as follows:

R_f (4% of methanol-methylene chloride-ammonium hydroxide): 0.38.

FAB MS: [m + H] at m/z 676.

HPLC: gradient 50% B to 80% B over 20 min, k' = 7.8.

Anal. Found: C, 66.83; H, 7.63; N, 8.10.

Preparation 7 Ethyl 2-(Phenoxyacetamido)benzoate (Formula C-3) Refer

to Chart C.

To a mixture of 0.0824 g of ethyl anthranilate hydrochl ride, 0.1248 g of dimethylaminopyridine, 0.0746 g of phenoxyacetic acid, and 5 ml of methylene chloride is added 0.074 ml of diethylphosphoryl-cyanide.

After 4 days the reaction is partitioned between methylene chloride, aq. sodium bicarbonate, and 3 N hydrochloric acid. The organic layers are filtered through sodium sulfate, concentrated, and the residue is chromatographed using 10% ethyl acetate-hexane to give 0.0553 g of crystalline title product.

Physical characteristics are as follows:

M.P.: 95.5-96.5°C.

MS: m/z at 299.

^{1}H-NMR (δ, $CDCl_3$): 1.40, 4.41, 4.64, 7.02-8.84.

Preparation 8 2-(Phenoxyacetamido) benzoic acid (Formula C-4) Refer to Chart C.

To 0.048 g of the title product of Preparation 7 in 5 ml of methanol is added 0.32 ml of 1 N sodium hydroxide. After stirring overnight, an additional 0.32 ml of 1 N sodium hydroxide is added. After 6 h, methanol is removed in vacuo, several ml's of water are added to the residue and the aqueous mixture is washed once with hexane. The aqueous layer is then acidified with 3 N hydrochloric acid and partitioned with ethyl acetate. The ethyl acetate layers are dried over magnesium sulfate and concentrated to 0.0434 g of a white solid. An aliquot is crystallized from methanol-methylene chloride-hexane to give the title product.

Physical characteristics are as follows:

M.P.: 191-192°C.

^{1}H-NMR (δ, $CDCl_3$ + methanol-d_4): 4.63, 7.0-5.84.

Example 3 2-(Phenoxyacetamido)benzoyl-LVA-Ile-Amp (Formula C-5) Refer to Chart C.

To 0.030 g of the title product of Preparation 8, 0.0435 g of LVA-Ile-Amp, 5 ml of methylene chloride, and 0.5 ml of dimethylformamide is added 0.0210 ml of triethylamine, followed by 0.0229 ml of diethyl-phosphorylcyanide. After stirring overnight, methylene chloride and dimethylformamide are removed in vacuo and the residue is chromato-graphed using 4% methanol-methylene chloride (ammonium hydroxide sat'd) to give 0.0465 g of the title product.

Physical characteristics are as follows:

R_f (8% methanol-methylene chloride-ammonium hydroxide): 0.46

FAB MS: [m + H] at m/z at 688.

HPLC: gradient 50% B to 70% B over 20 min, k' = 6.6.

Anal. Found: C, 67.82; H, 7.56; N, 10.11.

Preparation 9 Boc-Phe-3-(carbethoxy)benzamide (Formula D-3) Refer to Chart D.

To 1.03 g of ethyl 3-aminobenzoate, 2.09 g of Boc-Phe, 1.18 g of triethylamine, and 25 ml of methylene chloride is added 1.29 ml of diethylphosphorylcyanide, leading to an exotherm. After 5 min, the reaction is partitioned between methylene chloride, aq. sodium bicarbonate, 2 N hydrochloric acid, and brine. The organic layers are filtered through sodium sulfate. concentrated, and the residue is chromatographed using 15% ethyl acetate-hexane. The product is crystallized from methylene chloride and hexane to give 0.68 g of the title product.

Physical characteristics are as follows:

M.P.: 177.5-178.5°C.

$[\alpha]_D$ = -2 (0.195, ethanol).

^{1}H-NMR (δ, $CDCl_3$ + methanol-d_4): 1.40, 1.37, 3.10, 4.35, 4.5, 5.46, 7.23-7.92, 8.55.

Anal. Found: C, 66.78; H, 7.16; N, 6.81.

Preparation 10 Boc-Phe-3-(carboxy)benzamide (Formula D-4) Refer to Chart D.

The title product of Preparation 9 (0.32 g) is stirred in tetrahydrofuran-methanol with 1.16 ml of 1 N sodium hydroxide for 20 h. The solvents are then removed in vacuo, water is added, and the aq. mixture is washed with hexane. The aqueous layer is then acidified with 2 N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layers are washed with brine and dried over magnesium sulfate to give 0.31 g of crude product. The product is crystallized (or precipitated) from a mixture of ethyl acetate, methylene chloride, methanol, and hexane to give 0.194 g of the title product.

Physical characteristics are as follows:

M.P.: 206-208°C.

$[\alpha]_D$ = +1 (1.21, methanol).

Anal. Found: C, 65.26; H, 6.48; N, 7.17.

Example 4 3-(Boc-Phe-amido)benzoyl-LVA-Ile-Amp (Formula D-6) Refer

to Chart D.

To 0.0391 g of the title product of Preparation 10, 0.040 g of LVA-Ile-Amp, and 20 ml of methylene chloride is added 0.0161 ml of triethylamine, followed by 0.0175 ml of diethylphosphorylcyanide. After stirring over the weekend, the reaction mixture is concentrated and chromatographed using 4% methanol-methylene chloride (ammonium hydroxide sat'd). Due to a spill, 0.022 g of the title product was obtained.

Physical characteristics are as follows:

R^f (8% methanol-methylene chloride): 0.64.

FAB MS: [m + H] at m/z at 801.

HPLC: 50% A-50% B, k' = 10.3.

Anal. Found: C, 66.27; H, 8.00; N, 10.05.

Preparation 11 Ethyl 2-(Phenylthioethylcarboxamido)benzoate (Formula E-3) Refer to Chart E.

A mixture of 0.260 g of ethyl 2-aminobenzoate, 0.301 g of 3-(phenylthio)propionic acid, 0.255 g of 1-hydroxybenzotriazole, 0.389 g of dicyclohexylcarbodiimide, and 20 ml of methylene chloride is stirred overnight. DCU (dicyclohexylurea) is then filtered off and the filtrate is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate and chromatographed on silica gel using 1% methanol-methylene chloride to give 0.0859 g of the title product.

Physical characteristics are as follows:

MS: m/z at 329.

^{1}H-NMR (δ, $CDCl_3$): 1.50, 2.85, 3.40, 4.46, 7.15-7.65, 8.13, 8.79.

Anal. Found: C, 65.23; H, 5.83; N, 4.12.

Preparation 12 2-(Phenylthioethylcarboxamido)benzoic acid (Formula E-4) Refer to Chart E.

A mixture of 0.084 g of the title product of Preparation 11, 0.38 ml of 1 N sodium hydroxide, and 20 ml of ethanol is stirred at room temperature for 70 min. Ethanol is then removed in vacuo and the residue is partitioned between ethyl acetate and aq. hydrochloric acid and brine. The organic layers are filtered through sodium sulfate and taken to dryness to give 0.040 g of the title product.

Physical characteristics are as follows:

MS: m/z at 301.

Anal. Found: C, 63.49; H, 5.18; N, 4.59.

Example 5 2-(Phenylthioethylcarboxamido)benzoyl-LVA-Ile-Amp (Formula E-5) Refer to Chart E.

To 0.0275 g of the title product of Preparation 12 and 0.0419 g of LVA-Ile-Amp·2HCl in 5 ml of methylene chloride are added 0.0382 ml of triethylamine, followed by 0.0164 ml of diethylphosphorylcyanide and 0.5 ml of dimethylformamide. After stirring for 26 h, the solvents are removed in vacuo and the residue is chromatographed on silica gel using 4% methanol-methylene chloride (aq. ammonium hydroxide sat'd) to give 0.013 g of the title product.

Physical characteristics are as follows:

R_f (4% methanol-methylene chloride-ammonium hydroxide): 0.29.

MS: m/z at 716.

HPLC: 50% A-50% B, R' = 11.3.

Preparation 13 Ethyl 3-(Phenylthioethylcarboxamido)benzoate (Formula E-3) Refer to Chart E.

In the same manner and in the same amounts as for the title product of Preparation 11, 0.42 g of the title product is obtained.

Physical characteristics are as follows:

MS: m/z at 329.

^{1}H-NMR(δ, $CDCl_3$): 1.47, 2.75, 3.38, 7.30-8.04.

Preparation 14 3-(Phenylthioethylcarboxamido)benzoic acid (Formula E-4) Refer to Chart E.

A mixture of 0.40 g of the title product of Preparation 13, 75 ml of ethanol, 2.82 ml of 1 N sodium hydroxide, and 5 ml of methylene chloride is stirred for 2 h. The solvents are then removed in vacuo and the residue is found to be mostly starting material. The reaction is then stirred overnight in 80 ml of methanol and 1 ml of 1 N sodium hydroxide. After removal of solvent, the residue is acidified with aq. hydrochloric acid and partitioned with methylene chloride. The organic layers are taken to dryness, diethyl ether and hexane are added to the residue, and the resulting solid is collected to give 0.10 g of the title product.

Physical characteristics are as follows:

^{1}H-NMR (δ, $CDCl_3$ + methanol-d_4): 2.68, 3.30, 7.29-7.91.

Example 6 3-(Phenylthioethylcarboxamido)benzoyl-LVA-Ile-Amp (Formula E-6) Refer to Chart E.

To a mixture of 0.0371 g of the title product of Preparation 14, 0.0479 g of LVA-Ile-Amp·2HCl, 10 ml of dimethylf rmamide, and 5 ml of

methylene chloride are added 0.045 ml of triethylamine and 0.020 ml of diethylphosphorylcyanide. After stirring for 1.3 h, the solvents are removed in vacuo and the residue is chromatographed on silica gel using a gradient of 2% to 4% methanol-methylene chloride (ammonium hydroxide sat'd) to give 0.0529 g of the title product.

Physical characteristics are as follows:

MS: m/z at 717.

HPLC: 50%A-50%B, k' = 5.1.

Preparation 15 Ethyl 2-(Boc-Phe-amido)benzoate (Formula D-3) Refer to Chart D.

To 1.00 g of ethyl 2-aminobenzoate, 2.09 g of BOC-Phe, 1.06 g of 1-HOBt, and 100 ml of methylene chloride is added 1.62 g of dicyclohexylcarbodiimide. After stirring overnight, an additional 0.44 g of dicyclohexylcarbodiimide is added. The reaction is stirred for another 24 h and is then concentrated and filtered to remove DCU (dicyclohexylurea). The filtrate is partitioned between methylene chloride, 2 N hydrochloric acid, and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and chromatographed with 10% ethyl acetate-hexane to give 0.84 g of crystalline title product.

Physical characteristics are as follows:

M.P.: 110-115°C.

$[\alpha]_D$ = -56° (0.2675, ethanol).

^{1}H-NMR (δ, $CDCl_3$): 1.41, 1.37, 3.19, 4.32, 4.65, 5.00, 6.55, 6.95-7.65, 8.00, 8.75.

Anal. Found: C, 66.86; H, 6.98; N, 7.00.

Preparation 16 2-(Boc-Phe-amido)benzoic acid (Formula D-4) Refer to Chart D.

To 0.46 g of the title product of Preparation 15 in 25 ml of ethanol is added dropwise over several minutes 1.67 ml of 1 N sodium hydroxide. After stirring for 1 h, the reaction is concentrated, acidified with aq. hydrochloric acid, and partitioned between ethyl acetate and brine. The organic layers are dried over magnesium sulfate and concentrated in vacuo. The residue is crystallized from ethyl acetate and hexane to give 0.227 g of the title product.

Physical characteristics are as follows:

M.P.: 188-189°C.

MS: [m + H] at m/z 385.

$[\alpha]_D$ = -29° (0.975, methanol).

Anal. Found: C, 65.26; H, 6.28; N, 7.04.

Example 7 2-(Boc-Phe-amido)benzoyl-LVA-Ile-Amp (Formula D-5) Refer to Chart D.

To 0.0402 g of the title product of Preparation 16, 0.0412 g of LVA-Ile-Amp and 10 ml of methylene chloride are added 0.0166 ml of triethylamine and 0.0181 ml of diethylphosphorylcyanide. After stirring overnight, an additional 0.010 ml of triethylamine and 0.008 ml of diethylphosphorylcyanide are added and stirring is continued for an additional 2 days. The reaction mixture is then partitioned between methylene chloride and aq. ammonium bicarbonate and the organic layers are filtered through sodium sulfate and concentrated in vacuo. The residue is chromatographed using 4% methanol-methylene chloride (ammonium hydroxide sat'd) to give 0.0406 g of the title product.

Physical characteristics are as follows:

Rf (4% methanol-methylene chloride-ammonium hydroxide): 0.28 (bright blue fluorescence).

FAB MS: [m + H] at m/z 801.

HPLC: 45%A-55%B, k' = 8.8, 9.6 (17/83 ratio).

Anal. Found: C, 66.27; H; 8.20; N, 10.15.

Preparation 17 Methyl 2-aminonicotinate (Formula F-2) Refer to Chart F.

A solution of 0.78 g of 2-amino nicotinic acid in 70 ml of methanol/methylene chloride is stirred for 4 days. The solvent is then removed in vacuo and the residue is partitioned with methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate and taken to dryness to give 0.38 g of the title product.

Physical characteristics are as follows:

MS: m/z at 152.

^{1}H-NMR (δ, $CDCl_3$): 1.65, 3.88, 6.62, 8.12, 8.23.

Preparation 18 2-(Boc-Phe-amido)nicotinic acid, ethyl ester (Formula F-3) Refer to Chart F.

To 0.437 g of Boc-Phe and 0.125 g of the title product of Preparation 17 in 50 ml of methylene chloride are added 0.222 g of 1-HOBt (1-hydroxybenzotriazole) and 0.340 g of dicyclohexylcarbodiimide. After stirring for 5 days, the reaction mixture is partitioned between methylene chloride, aq. hydrochloric acid, and aq. sodium bicarbonate. The crude product is chromatographed on silica gel to give 0.0668 g of the title product.

Physical characteristics are as follows:

R_f (4% methanol-methylene chloride-ammonium hydroxide): 0.42.

MS: m/z at 399.

Preparation 19 2-Boc-Phe-amido)nicotinic acid (Formula F-4) Refer to Chart F.

A mixture of 0.0648 g of the title product of Preparation 18, 0.194 ml of 1 N sodium hydroxide, and 5 ml of methanol is stirred at room temperature for 1 h and then taken to dryness in vacuo. The residue is partitioned between diethyl ether and aq. hydrochloric acid and taken to dryness over magnesium sulfate to give 0.063 g of impure title product.

Example 8 2-(Boc-Phe-amido)nicotinoyl-LVA-Ile-Amp (Formula F-5) Refer to Chart F.

To 0.060 g of the title product of Preparation 19 (impure) and 0.078 g of LVA-Ile Amp·2HCl in 10 ml of methylene chloride is added 0.072 ml of triethylamine, followed by 0.031 ml of diethylphosphoryl-cyanide. After stirring for 2 days at room temperature, the reaction mixture is partitioned with chloroform and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and chromatographed on silica gel using a gradient of 4% to 6% methanol-methylene chloride (ammonium hydroxide sat'd) to give 0.0108 g of the title product.

Physical characteristics are as follows:

R_f (6% methanol-methylene chloride-ammonium hydroxide): 0.43.

FAB MS: [m + H] at m/z 802.

HPLC: 50%A-50%B, k' = 6.6.

Preparation 20 Ethyl 2-(Phenylthiomethyleneoxy)benzoate (Formula B-3) Refer to Chart B.

Sodium hydride (0.132 g, 60% in oil) is washed twice with hexane and then stirred with 2 ml of hexamethylphosphoramide. To this is added 0.500 g of ethyl salicylate. After 10 minutes, 0.525 g of chloromethylphenylsulfide is added. The reaction is stirred for 4 h and then partitioned between ethyl acetate and brine (three times). The organic layers are filtered through sodium sulfate, concentrated, and the crude product chromatographed on silica gel using 10% ethyl acetate-hexane to give 0.48 g of the title product as a clear liquid.

Physical characteristics are as follows:

^{1}H-NMR (δ, $CDCl_3$): 1.34, 4.33, 5.56, 7.02-7.83.

Preparation 21 2-(Phenylthiomethyleneoxy)benzoic Acid (Formula B-4) Refer to Chart B.

A mixture of 0.29 g of the title product of Preparation 20, 1.5 ml of 1 N sodium hydroxide, and 20 ml of methanol is stirred at room temperature overnight, after which an additional 1.5 ml of 1 N sodium hydroxide is added. The reaction is stirred an additional 30 h and then methanol is removed in vacuo. The residue is partitioned between diethyl ether and aq. hydrochloric acid and the organic layers are dried over magnesium sulfate to give 0.26 g of a crystalline solid. Recrystallization from diethyl ether-methylene chloride-hexane gives colorless crystals of the title product.

Physical characteristics are as follows:

M.P.: 70-70.5°C.

^{1}H-NMR (δ, $CDCl_3$): 5.63, 7.05-7.56, 8.20.

Example 9 2-(Phenylthiomethyleneoxy)benzoyl-LVA-Ile-Amp (Formula B-7) Refer to Chart B.

To 0.0764 g of the title product of Preparation 21, 0.1185 g of LVA-Ile-Amp·2HCl, and 30 ml of methylene chloride are added 0.106 ml of triethylamine, followed by 0.0445 ml of diethylphosphorylcyanide. After about a minute, 2 ml of dimethylformamide is added to obtain a homogeneous solution. After 2.5 h, the reaction mixture is partitioned between methylene chloride and aq. sodium bicarbonate and brine. The organic layers are filtered through sodium sulfate, concentrated, and the residue chromatographed on silica gel using 3% methanol-methylene chloride (ammonium hydroxide sat'd) to give 0.1305 g of the title product.

Physical characteristics are as follows:

R_f (4% methanol-methylene chloride-ammonium hydroxide): 0.35.

FAB MS: [m + H] at m/z.

HPLC: 45%A-55%B, k' = 6.1.

Preparation 22 N^{α}-(4-Carboxy)nicotinoyl-D-phenylalanine tert-butyl ester and/or N^{α}-(3-Carboxy)isonicotinoyl-D-phenylalanine tert-butyl ester (Formula L-4 and/or Formula L-3) Refer to Chart L.

To 0.2007 g of D-Phe-O-t-Bu in 10 ml of tetrahydrofuran and 2 ml of methylene chloride is added 0.1444 g of 3,4-pyridine bicarboxylic anhydride. After stirring for 3.5 hrs, the reaction mixture is partitioned between diethyl ether and brine. The organic layers are

dried over magnesium sulfate and the crude pr duct is chromat graphed on silica gel using 8% methanol-methylene chloride (acetic acid) to give 0.34 g of the title product as a white s lid.

Physical characteristics are as follows:

^{1}H-NMR (δ, $CDCl_3$): 1.42, 1.43, 3.23, 4.98, 6.92, 7.10, 7.22, 7.83, 8.70, 8.80, 9.18.

Example 10 4-[(1'R-tert-Butoxycarbonyl)phenethylaminocarbonyl]-nicotinoyl-LVA-Ile-Amp and/or 3-[(1'R-tert-Butoxycarbonyl)phenethylaminocarbonyl]isonicotinoyl-LVA-Ile-Amp (Formula L-6 and/or Formula L-7) Refer to Chart L.

To 0.040 g of the title product of Preparation 22, 0.0516 g of 2HCl-LVA-Ile-Amp, 3 ml of methylene chloride, and 0.25 ml of dimethylformamide are added 0.046 ml of triethylamine and 0.019 ml of diethylphosphorylcyanide. After stirring 20 hrs, the solvents are removed in vacuo and the residue is partitioned between methylene chloride and aq. sodium bicarbonate. The crude product is chromatographed on silica gel using 4% methanol-methylene chloride (ammonium hydroxide) to give 0.0292 g of the title product.

Physical characteristics are as follows:

Anal. Found: C, 66.67; H, 8.13; N, 10.41.

Preparation 23 N^{α}-(3-Carboxy)picolinoyl-D-phenylalanine tert-butyl ester and/or N^{α}-(2-Carboxy)nicotinoyl-D-phenylalanine tert-butyl ester (Formula M-3 and/or Formula M-4) Refer to Chart M.

To 0.2347 g of D-Phe-O-t-Bu in 5 ml of tetrahydrofuran is added 0.1688 g of 2,3-pyridine dicarboxylic anhydride. After stirring for 1.75 hrs, the reaction mixture is partitioned between diethyl ether and brine. The organic layers are dried over magnesium sulfate, concentrated, and the residue is chromatographed on silica gel using 8% methanol-methylene chloride (acetic acid) to give 0.46 g of the title product as a gum. The material is stored under high vacuum to remove residual acetic acid.

Physical characteristics are as follows:

^{1}H-NMR (δ, $CDCl_3$): 1.42, 3.22, 4.91, 7.17-7.28, 7.58, 8.65, 9.28.

Example 11 3-[(1'R-tert-Butoxycarbonyl)phenethylaminocarbonyl]picolinoyl-LVA-Ile-Amp and/or 2-[(1'R-tert-Butoxycarbonyl)phenethylaminocarbonyl]nicotinoyl-LVA-Ile-Amp (Formula M-6 and/or Formula M-7) Refer to Chart M.

To 0.040 g of the title product of Preparation 23, 0.0516 g of 2HCl-LVA-Ile-Amp, 3 ml of methylene chloride, and 0.25 ml of dimethylformamide are added 0.046 ml of triethylamine and 0.019 ml of diethylphosphorylcyanide. After stirring for 2.5 hrs, the solvents are removed and the residue is chromatographed on silica gel using 2% methanol-methylene chloride (ammonium hydroxide) to give 0.0378 g of the title product.

Physical characteristics are as follows:

Anal. Found: C, 66.58; H, 8.11; N, 10.26.

Preparation 24 m-(Phenethyloxy)benzoic acid, ethyl ester (Formula N-3) Refer to Chart N.

To 0.183 g of ethyl 3-hydroxybenzoate in 25 ml of acetonitrile is added 0.13 g of KH (20% in oil). After several minutes, about 0.06 g of 18-crown-6 is added, followed by 0.265 g of phenethyl bromide. After stirring overnight at room temperature, the reaction is heated at reflux for one week. Acetonitrile is then removed in vacuo and the residue is partitioned between diethyl ether and water. The organic layers are dried over magnesium sulfate, and the crude product is chromatographed using 5% ethyl acetate-hexane to give 0.030 g of the title product.

Physical characteristics are as follows:

^{1}H-NMR (δ, $CDCl_3$): 1.37, 3.10, 4.27, 7.0-7.7.

Preparation 25 m-(Phenethyloxy)benzoic acid (Formula N-4) Refer to Chart N.

To 0.0581 g of the title product of Preparation 24 in 2 ml of methanol is added 0.43 ml of 1 N sodium hydroxide. After stirring overnight, methanol is removed and the residue is acidified with 3 N hydrochloric acid and partitioned with methylene chloride. The organic layers are dried over magnesium sulfate and taken to dryness. The residue is crystallized from diethyl ether and hexane to give 0.0385 g of the title product.

Physical characteristics are as follows:

M.P.: 107-108°C.

MS: m/z at 242.

Preparation 26 m-(Phenethyloxy)benzoyl-Leuψ[CH(O-t-BDMS)CH_2]Val-Ile-Amp (Formula N-5) Refer to Chart N.

To 0.0338 g of the title product of Preparation 25, 0.0766 g of LVA (O-t-BDMS)-Ile-Amp, and 3 ml of methylene chloride is added 0.0233

ml of triethylamine, followed by 0.0254 ml of diethylphosphorylcyanide. After stirring for 2.25 h, the reaction is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate and taken to dryness to give 0.108 g of the title product.

Physical characteristics are as follows:

R_f (4% MeOH-96%-CH_2Cl_2-NH_4OH): 0.51.

Example 12 m-(Phenethyloxy)benzoyl-LVA-Ile-Amp (Formula N-6) Refer to Chart N.

To 0.108 g of the title product of Preparation 26 in 4 ml of tetrahydrofuran is added 2 ml of tetrabutylammonium fluoride (1 M in tetrahydrofuran). After 3.5 hr, tetrahydrofuran is removed and the residue is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and the residue chromatographed using a gradient of 2% to 4% methanol-methylene chloride to give 0.093 g of the title product.

Physical characteristics are as follows:

R_f (4% methanol, methylene chloride): 0.18.

^{1}H-NMR (δ, $CDCl_3$): 0.82-0.95, 3.09, 4.21, 4.50, 7.26, 8.48.

HPLC: gradient 50% B to 70% B over 15 min, k' = 17.0.

Anal. Found: C, 70.94; H, 8.16; N, 8.33.

Preparation 27 5S-tert-Butoxycarbonylamino-4S-tert-butyldimethylsilyloxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide (Formula H-3: X is 2(S)methylbutyl) Refer to Chart H.

To a solution of 0.390 g of Boc-Leuψ[CH(OSit-$BuMe_2$)CH_2]Val-OH, 0.0763 g of (s)-(-)-2-methylbutylamine, 0.118 g of 1-HOBt, and 10 ml of methylene chloride is added 0.180 of dicyclohexylcarbodiimide. After 3 hours an additional 0.005 g of the amine is added. Dicyclohexylurea is filtered off after a total of 24 hours of stirring at room temperature and the filtrate is extracted with methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and chromatographed on silica gel using 2% methanol-methylene chloride to give 0.414 g of the title product.

Physical characteristics are as follows:

TLC (4% methanol-methylene chloride): R_f = 0.74.

Preparation 28 5S-Amino-4S-tert-butyldimethylsilyloxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide (Formula H-4: X is 2(S)methylbutyl) Refer to Chart H.

A solution of 0.413 g of the title product of Preparation 27 in 10 ml of trifluoroacetic acid-methylene chloride (1:1) is stirred at room temperature for 10 minutes. Trifluoroacetic acid and methylene chloride are removed in vacuo and the residue is extracted four times with methylene chloride and two times with aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate and taken to dryness to give 0.323 g of the title product and a small amount of the de-silylated material.

Physical characteristics are as follows:

TLC (4% methanol-methylene chloride [ammonium hydroxide]): R_f = 0.35 (R_f = 0.09 for de-silylated product).

^{1}H-NMR (δ, $CDCl_3$): 0.05, 0.06, 0.89, 0.82-0.96, 1.43, 3.13, 5.85.

Preparation 29 2-(Phenylthiomethyleneoxy)benzoyl-Leuψ[CH(O-t-BDMS)CH_2]-Val-2S-methylbutylamide (Formula H-6: X is 2(S)methylbutyl) Refer to Chart H.

To 0.0684 g of 2-(phenylthiomethyleneoxy)benzoic acid, 0.0908 g of the title product of Preparation 28, and 10 ml of methylene chloride are added 0.0381 ml of triethylamine and 0.0415 ml of diethylphosphorylcyanide. After stirring for 1.33 hours, the reaction mixture is partitioned between methylene chloride and aq. sodium bicarbonate. The aqueous layers are filtered through sodium sulfate, concentrated, and the residue is chromatographed on silica gel using 1% methanol-methylene chloride to give 0.1430 g of the title product.

Physical characteristics are as follows:

R_f (2% methanol-methylene chloride): 0.49.

Example 13 2-(Phenylthiomethyleneoxy)benzoyl-LVA-2S-methylbutylamide (Formula H-7: X is 2(S)methylbutyl) Refer to Chart H.

To 0.1430 g of the title product of Preparation 29 in 3 ml of tetrahydrofuran is added 1 ml of 1 M (in tetrahydrofuran) tetra-n-butylammonium fluoride. After stirring overnight, solvent is removed in vacuo and the residue is partitioned between methylene chloride, water, and brine. The organic layers are filtered through sodium sulfate, concentrated, and the residue chromatographed on silica gel using 2% methanol-methylene chloride to give 0.118 g of the title product.

Physical characteristics are as follows:

FAB MS: [m + H] at m/z 543.

HPLC: 40% A-60%B; k' = 6.2.

Anal. Found: C, 67.89; H, 8.78; N, 5.01.

Preparation 30 5S-tert-Butoxycarbonylamino-4S-tert-butyldimethylsilyloxy-2S-isopropyl-7-methyloctanoyl-methylamide (Formula I-3) Refer to Chart I.

To a mixture of 0.250 g of the compound of formula I-1, 0.0834 g of 1-HOBt, 0.0624 g of triethylamine, 0.0416 g of methylamine hydrochloride, 2 ml of dimethylformamide, and 8 ml of methylene chloride is added 0.1273 g of dicyclohexylcarbodiimide. The reaction is stirred at room temperature for 2 days and then methylene chloride and dimethylformamide are removed in vacuo. Ethyl acetate is added to the residue and the solids are filtered off. The filtrate is taken to dryness in vacuo and the residue is extracted with methylene chloride and two times with aqueous sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and chromatographed on silica gel using 1% methanol-9% ethyl acetate-90% methylene chloride to give 0.2207 g of the title product.

Physical characteristics are as follows:

TLC (1% methanol-9% ethyl acetate-90% methylene chloride: R_f = 0.38.

^{1}H-NMR (δ, $CDCl_3$): 0.08, 0.89, 0.89-0.99, 1.44, 2.70, 2.76, 3.65, 4.5, 6.8.

Preparation 31 5S-Amino-4S-tert-butyldimethylsilyloxy-2S-isopropyl-7-methyloctanoyl-methylamide (Formula I-4) Refer to Chart I.

A solution of 0.737 g of the title product of Preparation 30 in 25 ml of trifluoroacetic acid-methylene chloride (1:1, v/v) is stirred for 30 minutes. Trifluoroacetic acid and methylene chloride are then removed in vacuo and the residue is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and the residue is chromatographed on silica gel using 5% methanol-methylene chloride (ammonium hydroxide sat'd) to give 0.492 g of the title product.

Physical characteristics are as follows:

R_f (8% methanol-methylene chloride-ammonium hydroxide): 0.53.

Preparation 32 2-(Phenylthiomethyleneoxy)benzoyl-Leuψ[CH(O-t-BDMS)CH_2]-Val-methylamide (Formula I-6) Refer to Chart I.

To 0.0500 g of 2-(phenylthiomethyleneoxy)benzoic acid, 0.05740 g

of the title product of Preparation 31, and 5 ml of methylene chloride are added 0.028 ml of triethylamine and 0.030 ml of diethylphosphoryl-cyanide. After stirring overnight, the reaction mixture is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and the residue is chromatographed on silica gel using 2% methanol-methylene chloride to give 0.10 g of the title product.

Physical characteristics are as follows:

R_f (4% methanol-methylene chloride): 0.38.

Example 14 2-(Phenylthiomethyleneoxy)benzoyl-LVA-methylamide (Formula I-7) Refer to Chart I.

To 0.096 g of the title product of Preparation 32 in 2 ml of tetrahydrofuran is added 0.5 ml of 1 M (in tetrahydrofuran) tetra-n-butylammonium fluoride. After stirring for 2 hours, tetrahydrofuran is removed in vacuo and the residue is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and the residue chromatographed on silica gel using 2% methanol-methylene chloride to give 0.0757 g of the title product.

Physical characteristics are as follows:

HPLC: 55% A-45%B; $k' = 6.8$.

Anal. Found: C, 66.72; H, 7.95; N, 5.65.

Preparation 33 5S-tert-Butoxycarbonylamino-4S-tert-butyldimethyl-silyloxy-2S-isopropyl-7-methyloctanoyl-n-butylamide (Formula H-3: X is n-butyl) Refer to Chart H.

To a solution of 0.10 g of the compound of formula H-1 and 0.0164 g of n-butylamine in 6 ml of methylene chloride is added 0.044 ml of diethylphosphorylcyanide and 0.040 ml of triethylamine. After stirring at room temperature for 30 minutes the reaction is extracted with methylene chloride, aq. sodium bicarbonate and 0.1 N hydrochloric acid. The organic layers are filtered through sodium sulfate and concentrated. The residue is chromatographed on silica gel using 2% methanol-methylene chloride to give 0.0885 g of the title product

Physical characteristics are as follows:

TLC (4% methanol-methylene chloride): $R_f = 0.42$.

^{1}H-NMR (δ, $CDCl_3$): 0.09, 0.89, 1.44, 3.20, 3.64, 4.45, 5.65.

Preparation 34 5S-Amino-4S-tert-butyldimethylsilyloxy-2S-isopropyl-7-methyloctanoyl-n-butylamide (Formula H-4: X is n-butyl)

Refer to Chart H.

A solution of 0.0885 g of the title product of Preparation 33 in 10 ml of trifluoroacetic acid-methylene chloride (1:1) is prepared for 15 minutes. Trifluoroacetic acid and methylene chloride are then removed in vacuo and the residue is extracted with methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and the residue chromatographed on silica gel (10 g) using 4% methanol-methylene chloride (ammonium hydroxide sat'd) to give 0.0624 g of the title product.

Physical characteristics are as follows:

TLC (4% methanol-methylene chloride-ammonium hydroxide sat'd): R_f = 0.64.

^{1}H-NMR (δ, $CDCl_3$): 0.06, 0.89, 1.90, 2.65, 3:20, 3.35, 6.90.

Preparation 35 2-(Phenylthiomethyleneoxy)benzoyl-Leuψ[O-t-BDMS)CH_2]Val-n-butylamide (Formula H-6: X is n-butyl) Refer to Chart H.

To 0.0500 g of 2-(phenylthiomethyleneoxy)benzoic acid, 0.0641 g of the title product of Preparation 34, and 5 ml of methylene chloride are added 0.028 ml of triethylamine and 0.030 ml of diethylphosphoryl-cyanide. After stirring overnight, the reaction mixture is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and the residue is chromatographed on silica gel using 2% methanol-methylene chloride to give 0.109 g of the title product.

Physical characteristics are as follows:

R_f (4% methanol-methylene chloride): 0.59.

Example 15 2-(Phenylthiomethyleneoxy)benzoyl-LVA-n-butylamide (Formula H-7: X is n-butyl) Refer to Chart H.

In the same manner as described in Example 14, 0.0808 g of the title product is prepared from 0.1029 g of the title product of Preparation 35.

Physical characteristics are as follows:

FAB MS: [m + H] at m/z 529.

HPLC: 45% A-55% B; k' = 6.4.

Anal. Found: C, 68.35: H, 8.45; N, 5.25.

Preparation 36 Methyl 3-(phenylthiomethyleneoxy)picolinate (Formula J-4) Refer to Chart J.

A mixture of 0.18 g of methyl 3-hydroxypicolinate, 0.17 ml of

chloromethylphenyl sulfide, 0.178 g of potassium carbonate, and 10 ml of dimethylformamide is stirred at room temperature for 20 hours. The dimethylformamide is then removed in vacuo and the residue is partitioned between methylene chloride and 1 N sodium hydroxide. The organic layers are filtered through sodium sulfate, concentrated, and the crude material is chromatographed on silica gel using 2% methanol-methylene chloride to give 0.1222 g of the title product.

Physical characteristics are as follows:

^{1}H-NMR (δ, $CDCl_3$): 1.56, 3.94, 5.58, 7.24-7.43, 8.38.

Preparation 37 3-(Phenylthiomethyleneoxy)picolinic acid (Formula J-5) Refer to Chart J.

To 0.122 g of the title product of Preparation 36 in 5 ml of methanol is added 0.7 ml of 1 N potassium hydroxide. After stirring for 5.5 hours at room temperature, methanol is removed in vacuo. Two to three mls of water are added, followed by 0.35 ml of 2 N hydrochloric acid. The aqueous mixture is then partitioned with methylene chloride and the organic layers are filtered through sodium sulfate and concentrated to dryness. The crude product is crystallized from methylene chloride and hexane to give 0.0803 g of the title product.

Physical characteristics are as follows:

MS: m/z at 261.

Anal. Found: C, 59.62; H, 4.34; N, 5.45.

Example 16 3-(Phenylthiomethyleneoxy)picolinoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-L-isoleucyl-2-(amidomethyl)pyridine (Formula J-7) Refer to Chart J.

To 0.0459 g of the title product of Preparation 37, 0.0829 g of 2HCl-LVA-Ile-Amp, 5 ml of dimethylformamide, and 2 ml of methylene chloride are added 0.0743 ml of triethylamine and 0.031 ml of diethylphosphorylcyanide. After stirring at room temperature for 2 hours, the reaction is stored overnight in the refrigerator. The solvents are then removed in vacuo and the residue is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated and the crude product is chromatographed on silica gel using 4% methanol-methylene chloride (ammonium hydroxide) to give 0.0893 g of the title product.

Physical characteristics are as follows:

FAB MS: [m + H] at m/z 678.

HPLC: 30% A, 70% B, k' = 5.4.

Anal. Found: C, 65.40; H, 7.53; N, 10.18.

Preparation 38 Ethyl 2-(phenoxyethyleneoxy)benzoate (Formula K-3) Refer to Chart K.

A mixture of 2.66 g of beta-bromophenetole, 2.00 g of ethyl 2-hydroxysalicylate, 1.83 g of potassium carbonate, and 25 ml of dimethylformamide is stirred at room temperature for 4 days. The solvent is then removed in vacuo and the residue is partitioned between methylene chloride, water, and brine. The organic layers are filtered through sodium sulfate and concentrated. The crude material is chromatographed on silica gel using 10% ethyl acetate-hexane to give 3.03 g of crystalline title product.

Physical characteristics are as follows:

M.P.: 82-84°C.

Anal. Found: C, 71.35; H, 6.46.

Preparation 39 2-(Phenoxyethyleneoxy)benzoic acid (Formula K-4) Refer to Chart K.

To 0.93 g of the title product of Preparation 38 in 50 ml of methanol and 1 ml of methylene chloride is added 4.87 g of 1 N sodium hydroxide. After stirring at room temperature for 1.5 hours, the reaction mixture is heated at reflux for 12 hours, then allowed to cool. The solvents are removed in vacuo and the residue is partitioned between methylene chloride and several mls of water containing 2.5 ml of 2 N hydrochloric acid. The organic layers are filtered through sodium sulfate and concentrated. The crude product is crystallized from methylene chloride-hexane to give 0.82 g of the title product.

Physical characteristics are as follows:

M.P.: 80-81°C.

Example 17 2-(Phenoxyethyleneoxy)benzoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-L-isoleucyl-2-(amidomethyl)-pyridine (Formula K-6) Refer to Chart K.

To 0.0559 g of the title product of Preparation 39, 0.0912 g of 2HCl-LVA-Ile-Amp, 2 ml of dimethylformamide, and 3 ml of methylene chloride are added 0.082 ml of triethylamine and 0.034 ml of diethylphosphorylcyanide. After stirring at room temperature for 2 hours, the reaction mixture is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate, concentrated, and the residue is chromatographed on silica gel using 4% methanol-methylene chloride (ammonium hydroxide) to give

0.1029 g of the title product.

Physical characteristics are as follows:

FAB MS: $[m + H]^+$ at m/z 675.

Anal. Found: C, 68.86; H, 7.97; N, 8.55.

Preparation 40 5S-tert-Butoxycarbonylamino-4S-tert-butyldimethylsilyloxy-2S-isopropyl-6-cyclohexylhexanoyl-methylamide (Formula P-3) Refer to Chart P.

To 0.0620 g of Boc-Chaψ[CH(O-t-BDMS)CH_2]Val-OH the compound of formula P-1, 0.00905 g of methylamine hydrochloride, and 4 ml of methylene chloride are added 0.042 ml of triethylamine and 0.025 ml of diethylphosphorylcyanide. After stirring for 24 hours, the reaction mixture is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate and concentrated. The residue is chromatographed on silica gel using 90% methylene chloride-9% ethyl acetate-1% methanol to give 0.064 g of the title product.

Physical characteristics are as follows:

R_f (90% methylene chloride-9% ethyl acetate-1% methanol): 0.38.

Preparation 41 5S-Amino-4S-tert-butyldimethylsilyloxy-2S-isopropyl-6-cyclohexylhexanoyl-methylamide (Formula P-4) Refer to Chart P.

To 0.064 g of the title product of Preparation 40 is added 4 ml of trifluoroacetic acid-methylene chloride (1:1 v/v). After stirring for 20 minutes, trifluoroacetic acid and methylene chloride are removed in vacuo and the residue is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate and concentrated to dryness to give 0.048 g of the title product.

Preparation 42 2-(Phenylthiomethyleneoxy)benzoyl-5S-amino-4S-tert-butyldimethylsilyloxy-2S-isopropyl-6-cyclohexylhexanoyl-methylamide (Formula P-6) Refer to Chart P.

To 0.0376 g of 2-(phenylthiomethyleneoxy) benzoic acid, 0.048 g of the title product of Preparation 41, and 2 ml of methylene chloride are added 0.022 ml of triethylamine and 0.024 ml of diethylphosphoryl-cyanide. After stirring at room temperature for 1.5 hours, the reaction mixture is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate and concentrated. The residue is chromatographed on silica gel

using 90% methylene chloride-9% ethyl acetate-1% methanol to give 0.0760 g of the title product.

Physical characteristics are as follows:

R_f (90% methylene chloride-9% ethyl acetate-1% methanol): 0.31.

Example 18 2-(Phenylthiomethylenoxy)benzoyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexylhexanoyl-methylamide (Formula P-7) Refer to Chart P.

To 0.0760 g of the title product of Preparation 42 in 2 ml of tetrahydrofuran is added 0.5 ml of n-tetrabutylammonium fluoride (1 M in tetrahydrofuran). After stirring for 1 hour, tetrahydrofuran is removed in vacuo and the residue is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate and concentrated. The residue is chromatographed on silica gel using 2% methanol-methylene chloride to give 0.0609 g of the title product.

Physical characteristics are as follows:

FAB MS: [m + H] at m/z 527.

HPLC: 25% A - 75% B; k' = 6.1.

Anal. Found: C, 68.21; H, 8.19; N, 5.11.

Preparation 43 1-Hydroxy-1-(2,2-dimethyl-3-tert-butyloxycarbonyl-4(S)-cyclohexylmethyl-5(R)-oxazolidinyl)-3-methylbutane (Formula Q-2) Refer to Chart Q.

To 5.09 ml of 2 M (in diethyl ether) isobutylmagnesium chloride in 10 ml of dry tetrahydrofuran at -15°C is added 1.658 g of the aldehyde of formula Q-1 prepared by a procedure similar to that described in PCT application, Serial No. 000.291, filed 13 February 1987 (about 10:1 5R:5S) in 10 ml of dry tetrahydrofuran (rinsed two times with 5 ml tetrahydrofuran). After stirring at -15°C for 50 minutes, the reaction mixture is poured onto cold sat'd aq. ammonium chloride. The material is partitioned with diethyl ether and washed with sat'd aq. sodium bicarbonate and two times with brine. The organic layers are dried over magnesium sulfate, concentrated, and the residue chromatographed on 500 ml of silica gel using a gradient of 0.5% methanol to 1% methanol-methylene chloride to give 0.60 g of the title product.

Physical characteristics are as follows:

MS: m/z at 383.

Preparation 44 2(S)-Amino-1-cyclohexyl-3(R),4-dihydroxy-6-methylheptane (Formula Q-3) Refer to Chart Q.

To 1 ml of ice-cooled methanol is added 0.064 ml of acetyl chloride. After stirring at room temperature for 5 minutes, the acetyl chloride-methanol mixture is added, using a 1 ml methanol rinse, to 0.0695 g of the title product of Preparation 43 in 1 ml of methanol. The reaction is stirred overnight and then an additional 0.032 ml of acetyl chloride in methanol is added. After stirring an additional 3 hours, 1 g of Amberlyst A-21 resin (weakly basic), which had been previously washed three times with methanol, is added to the reaction. After stirring for 45 minutes, the resin is filtered off (rinsing well with methanol) and the filtrate is taken to dryness to give 0.0495 g of crude material. Chromatography (silica gel) using 5% methanol-10% methanol-methylene chloride (ammonium hydroxide sat'd) gives 0.0374 g of the title product as a colorless solid.

Physical characteristics are as follows:

Anal. Found: C, 67.79; H, 12.12; N, 5.71.

Example 19 2-(Phenylthiomethyleneoxy)benzoyl-2S-amino-1-cyclohexyl-3R,4-dihydroxy-6-methylheptane (Formula Q-5) Refer to Chart Q.

To 0.012 g of the title product of Preparation 44, 0.0192 g of 2-(phenylthiomethyleneoxy) benzoic acid, and 2 ml of methylene chloride are added 0.011 ml of triethylamine and 0.012 ml of diethylphosphoryl-cyanide. After stirring for 2 hours, the reaction mixture is partitioned between methylene chloride and aq. sodium bicarbonate. The organic layers are filtered through sodium sulfate and taken to dryness in vacuo. The residue is chromatographed on silica gel using 1% methanol-methylene chloride affording a poor separation of a slower moving impurity. The material is re-chromatographed using 20% ethyl acetate-hexane to give 0.0170 of the title product.

Physical characteristics are as follows:

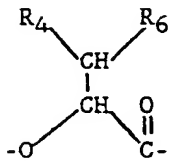
R_f (2% methanol-methylene chloride): 0.61.

FAB MS: [m + H] at m/z 485.

HPLC: 10% A - 90% B; k' = 6.9.

FORMULA CHART

$$X\text{-}A_6\text{-}B_7\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}G_{12}\text{-}H_{13}\text{-}I_{14}\text{-}Z \qquad I$$



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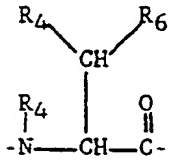

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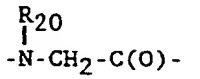

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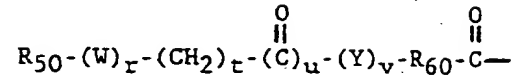

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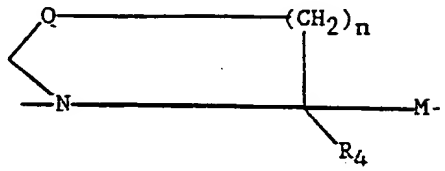

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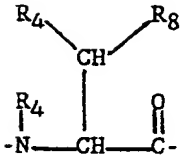

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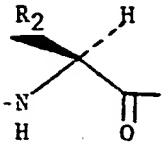

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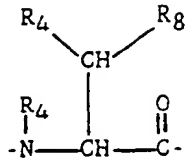

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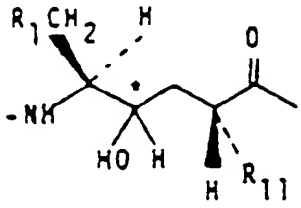

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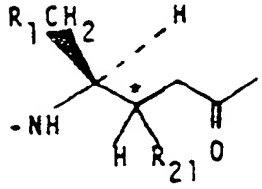

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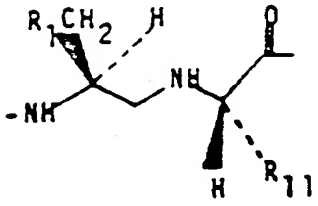

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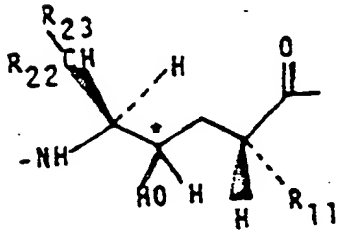

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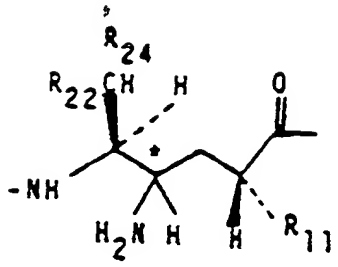

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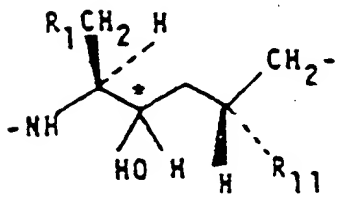

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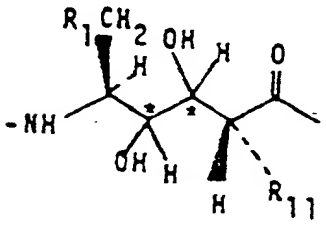

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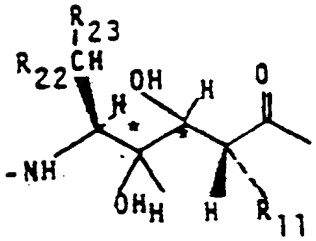
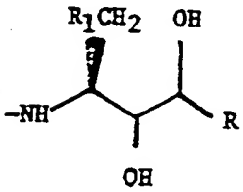


XL_{6g}



XL_{6h}

CHART A

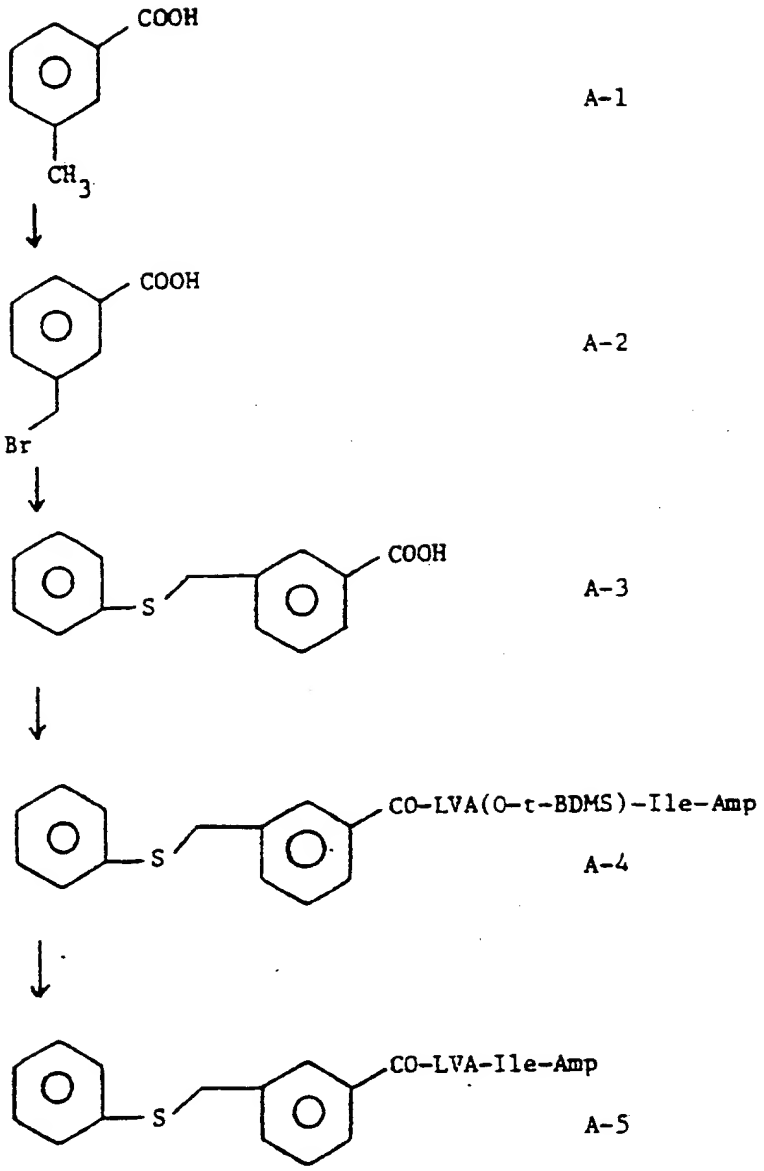

COOH
CH3
A-1
COOH
Br
A-2
S
COOH
A-3
S
CO-LVA(O-t-BDMS)-Ile-Amp
A-4
S
CO-LVA-Ile-Amp
A-5

CHART B

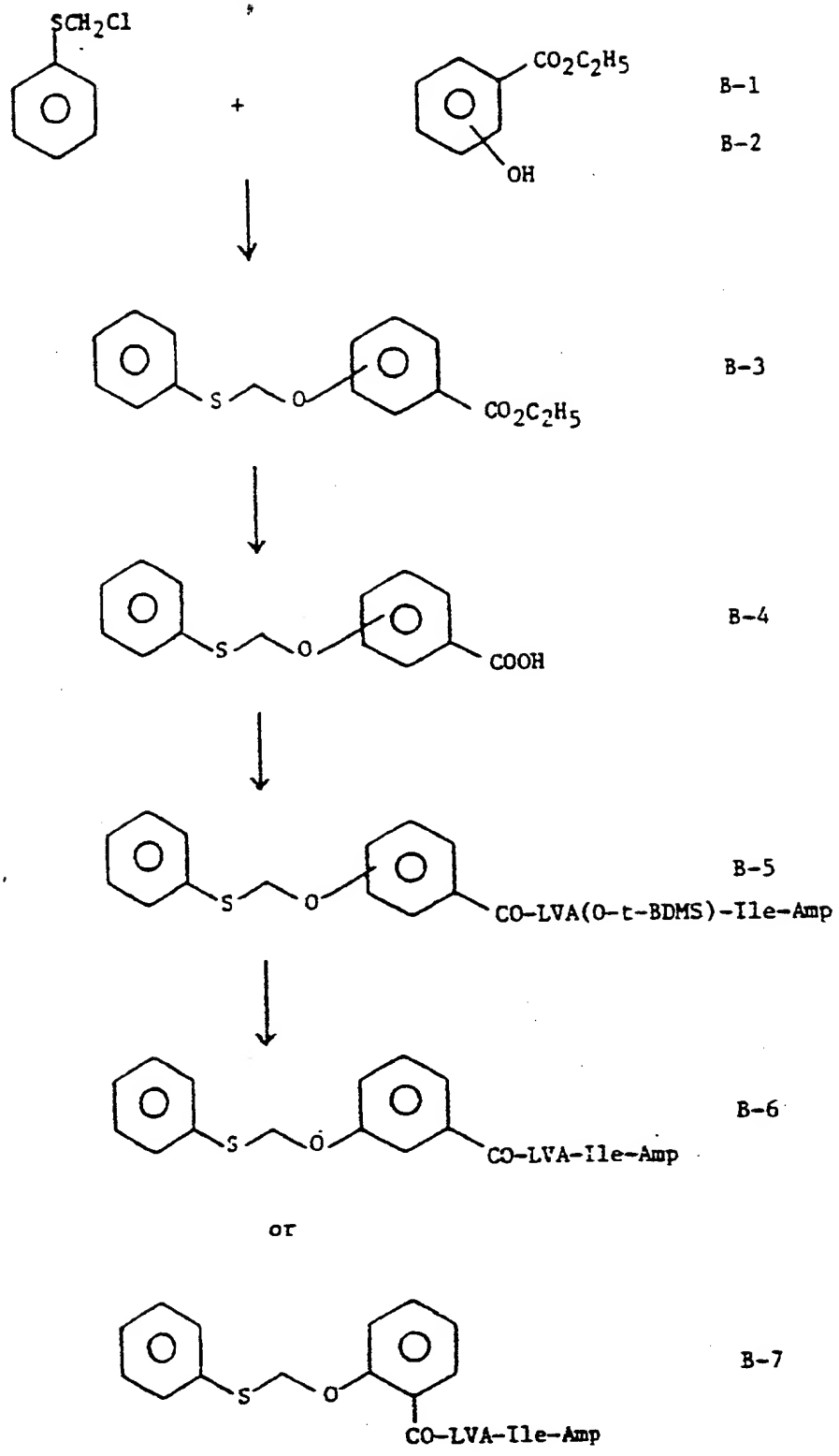

SCH2Cl
CO2C2H5
OH
B-1
B-2
S
O
CO2C2H5
B-3
COOH
B-4
CO-LVA(O-t-BDMS)-Ile-Amp
B-5
CO-LVA-Ile-Amp
B-6
or
CO-LVA-Ile-Amp
B-7

CHART C

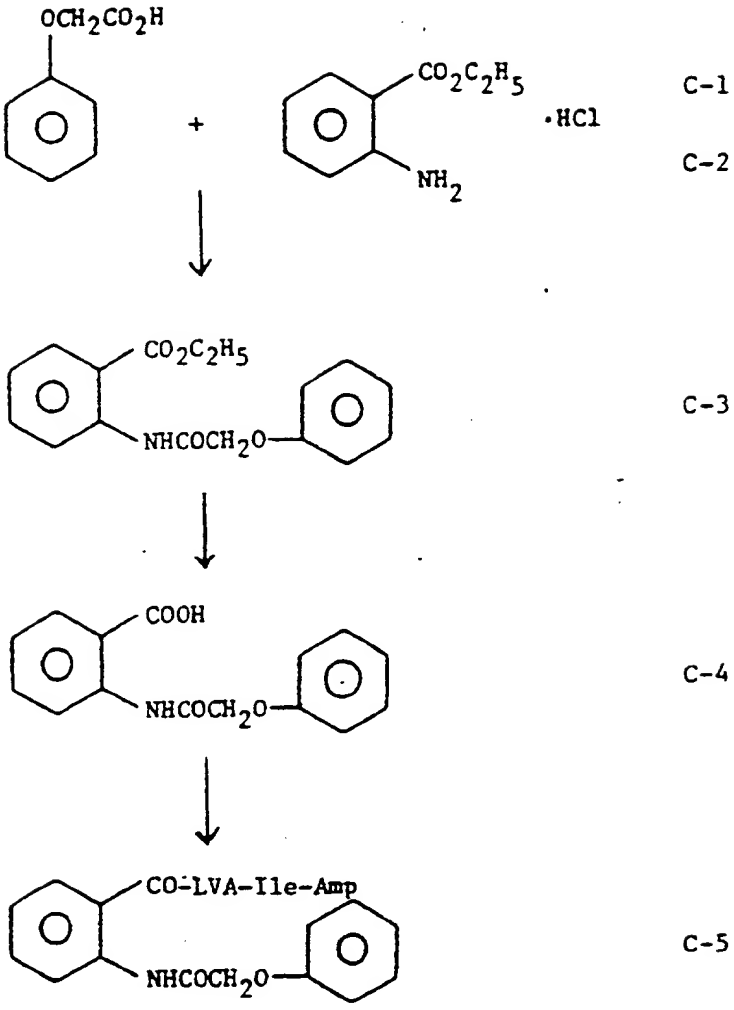
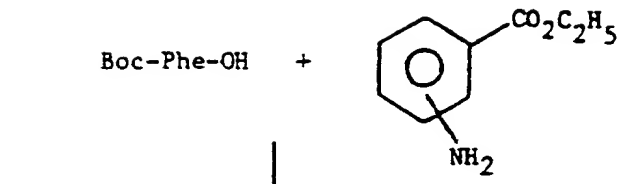
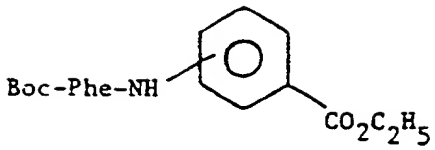

OCH2CO2H
CO2C2H5
·HCl
NH2
C-1
C-2
CO2C2H5
NHCOCH2O
C-3
COOH
NHCOCH2O
C-4
CO-LVA-Ile-Amp
NHCOCH2O
C-5

CHART D

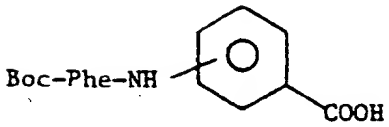


D-1

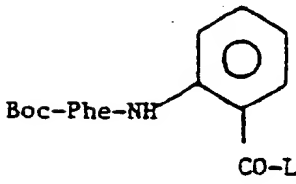
D-2



D-3

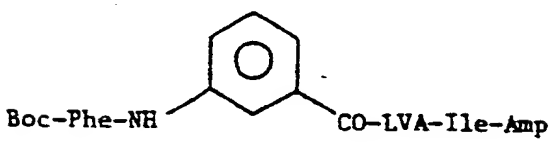


D-4



D-5

or



D-6

CHART E

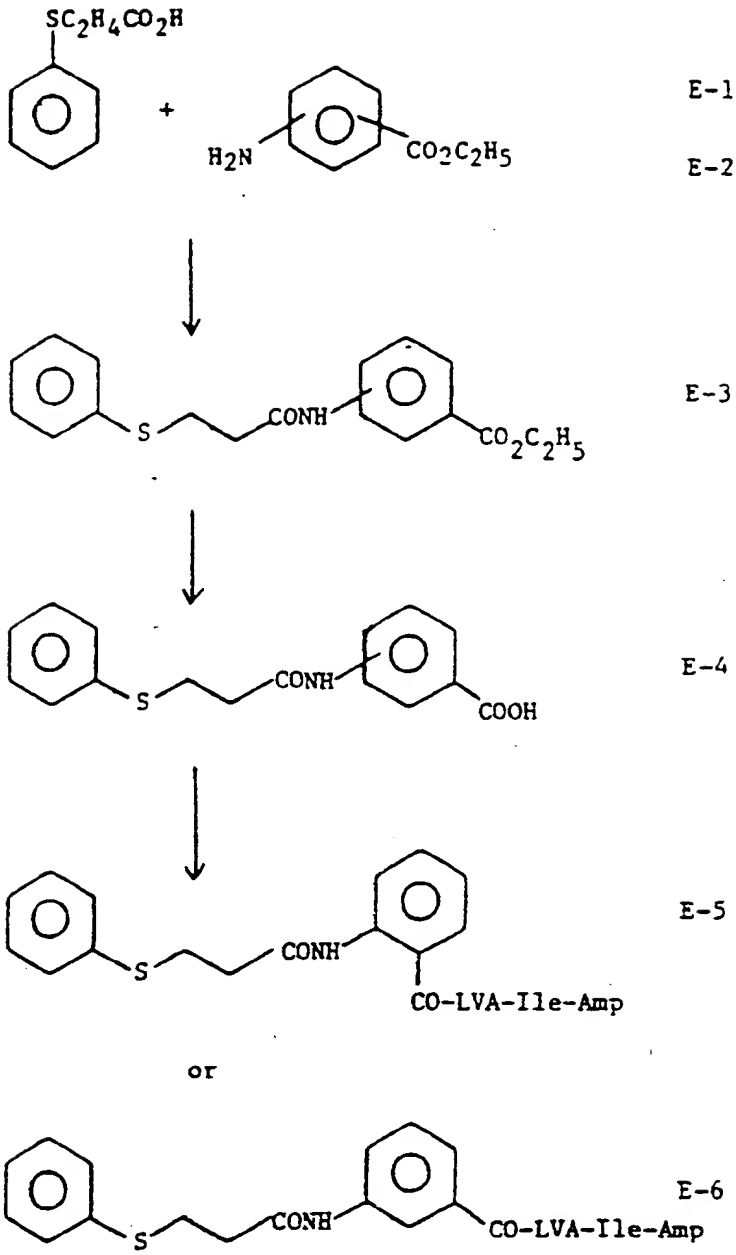

SC2H4CO2H
H2N
CO2C2H5
E-1
E-2
S
CONH
CO2C2H5
E-3
S
CONH
COOH
E-4
S
CONH
CO-LVA-Ile-Amp
E-5
or
S
CONH
CO-LVA-Ile-Amp
E-6

CHART F

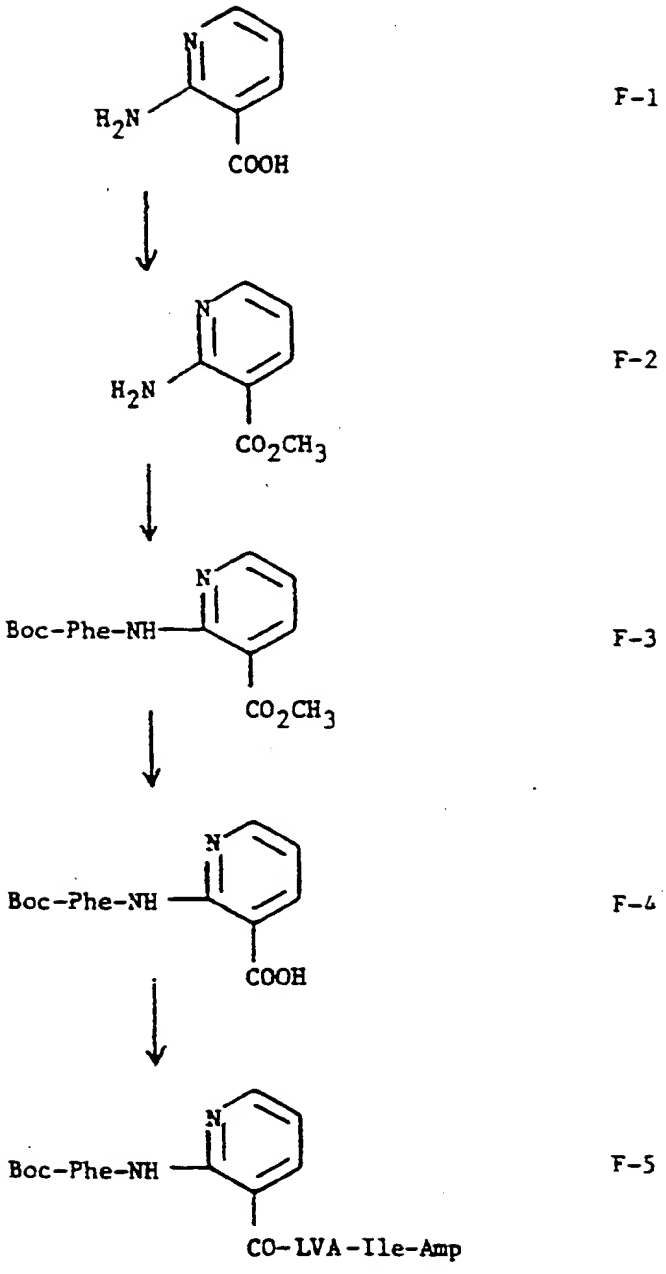


CHART G

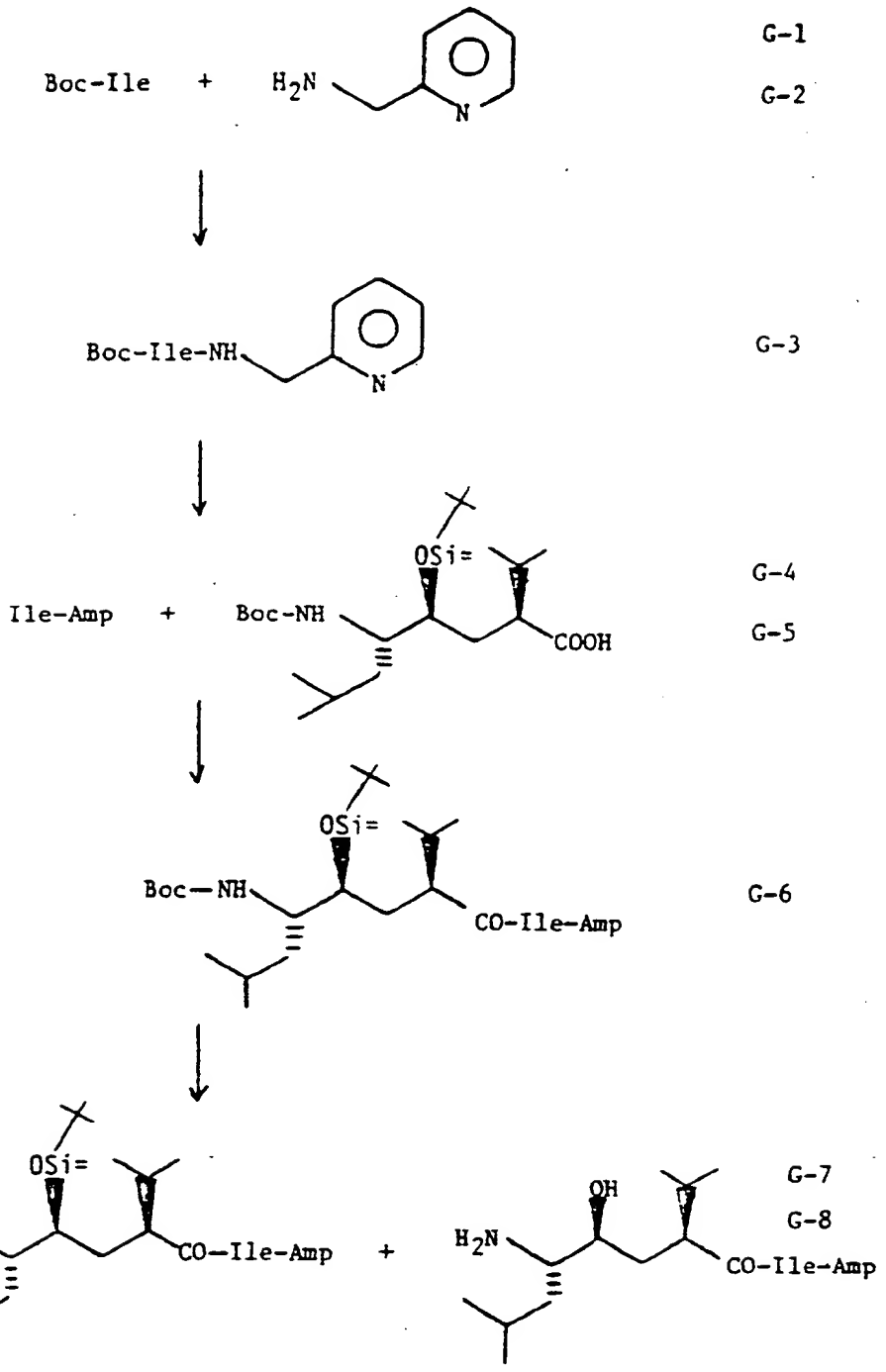

Boc-Ile + H_2N
N
G-1
G-2
Boc-Ile-NH
N
G-3
Ile-Amp + Boc-NH
OSi=
COOH
G-4
G-5
Boc—NH
OSi=
CO-Ile-Amp
G-6
H_2N
OSi=
CO—Ile-Amp +
OH
H_2N
CO-Ile-Amp
G-7
G-8

CHART H

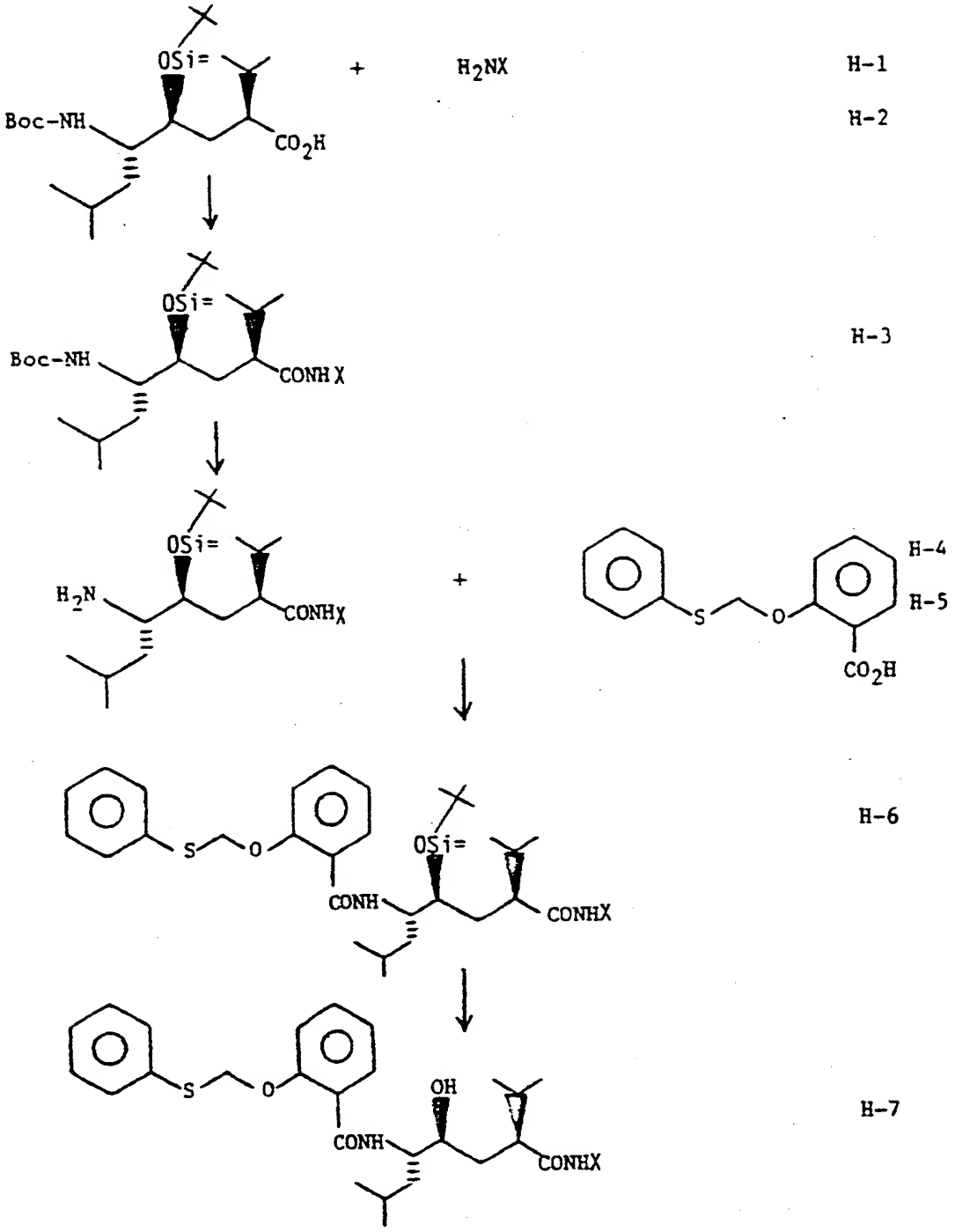
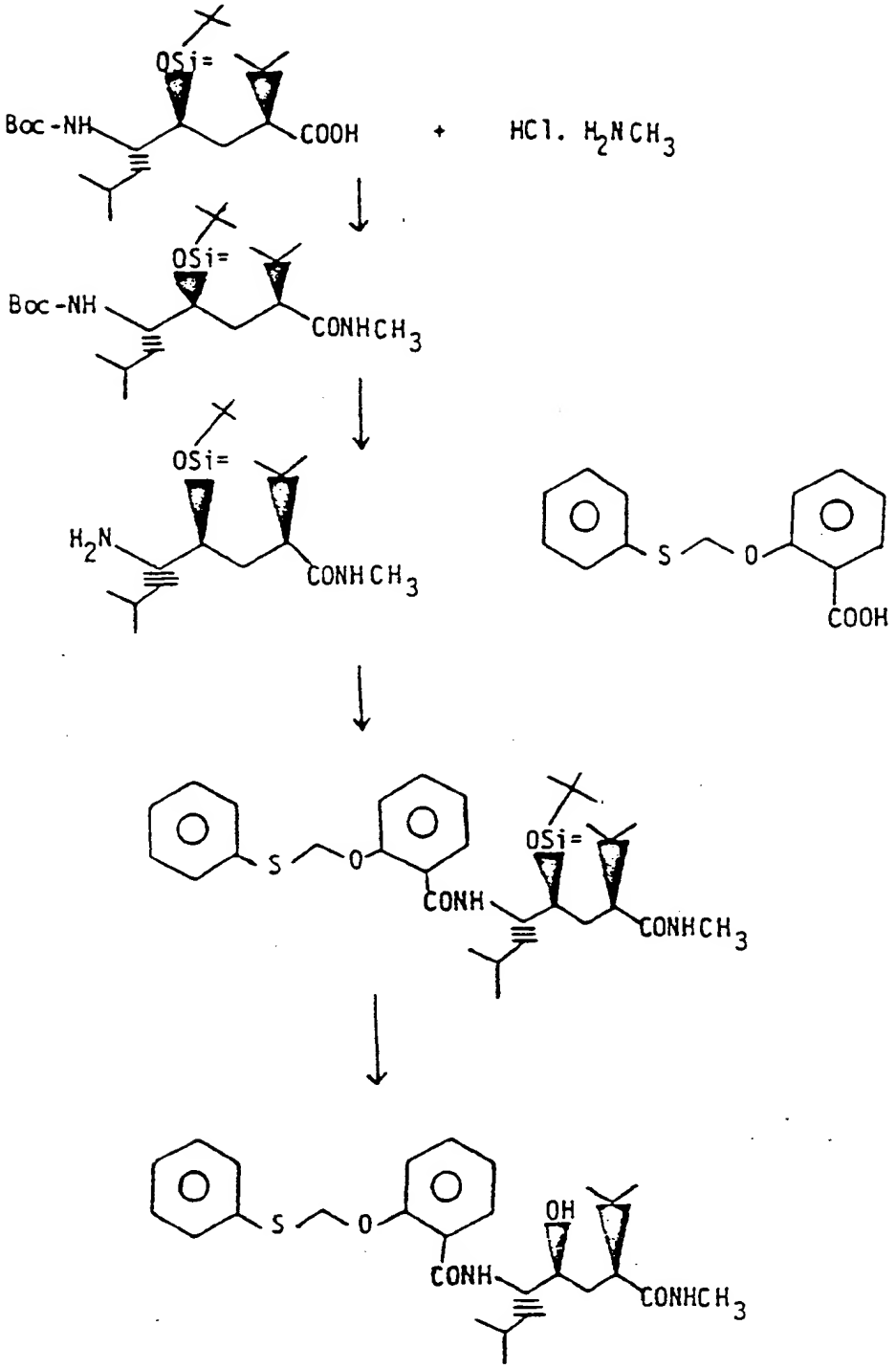
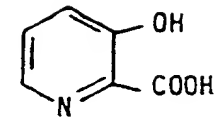

OSi=
Boc-NH
CO_2H
+
H_2NX
H-1
H-2
OSi=
Boc-NH
CONH X
H-3
OSi=
H_2N
CONHX
+
S
O
H-4
H-5
CO_2H
S
O
OSi=
CONH
CONHX
H-6
S
O
OH
CONH
CONHX
H-7

CHART I

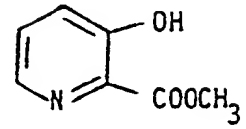


I-1
I-2
I-3
I-4
I-5
I-6
I-7

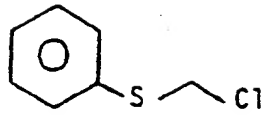
CHART J



J-1

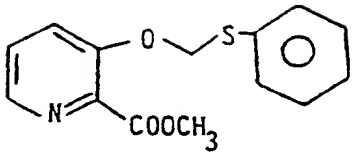


+

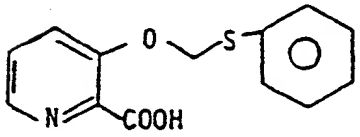


J-2

J-3



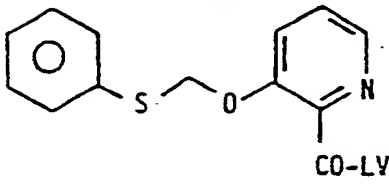
J-4



+ LVA-Ile-Amp

J-5

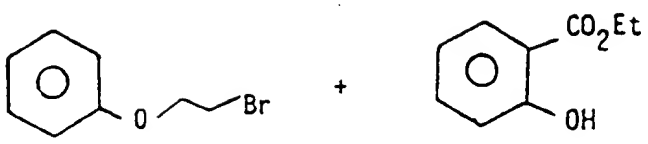
J-6



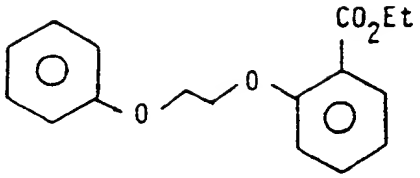
J-7

CO-LVA-Ile-Amp

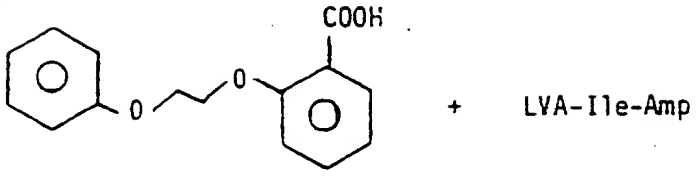
CHART K



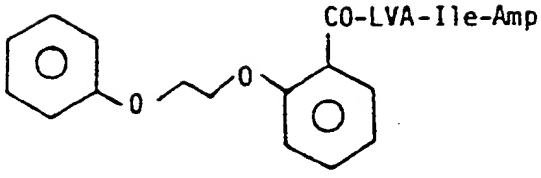
K-1
K-2



K-3



K-4
K-5



K-6

CHART L

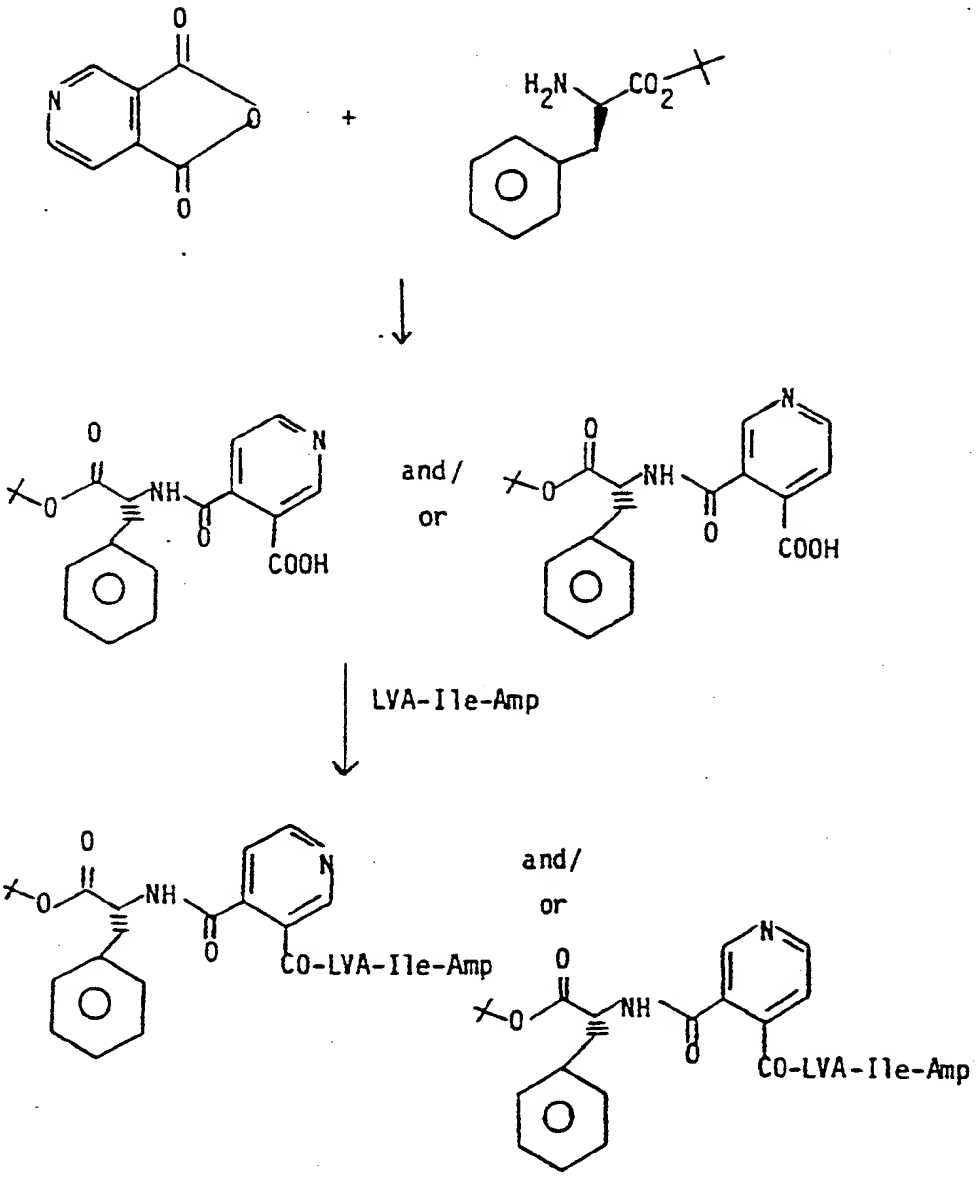
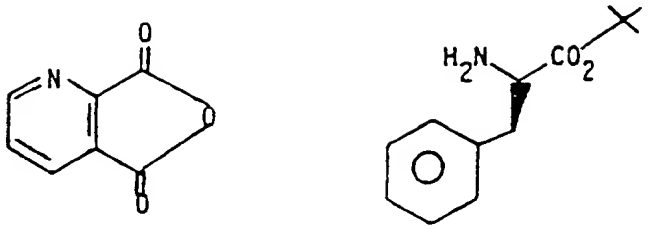
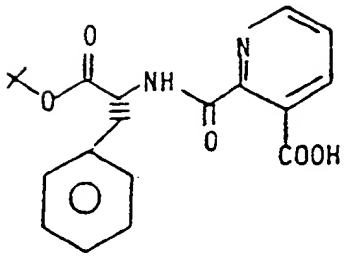

L-1
L-2
and/
or
L-3
L-4
LVA-Ile-Amp
L-5
and/
or
L-6
L-7
CO-LVA-Ile-Amp
CO-LVA-Ile-Amp

CHART M



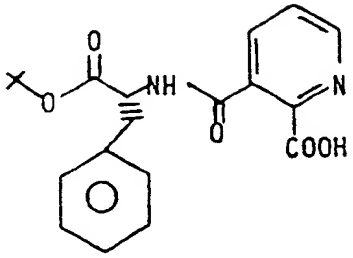
M-1

M-2



M-3

and/or



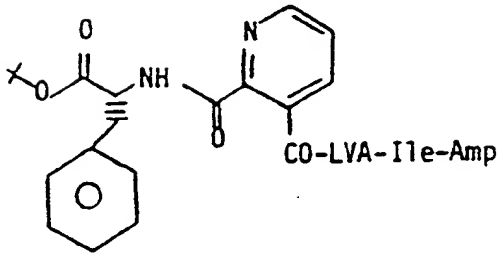
M-4

LVA-Ile-Amp

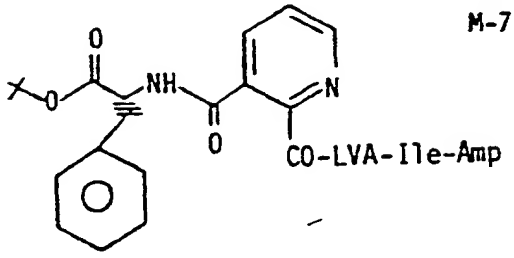
M-5

and/

or



M-6



M-7

CHART N

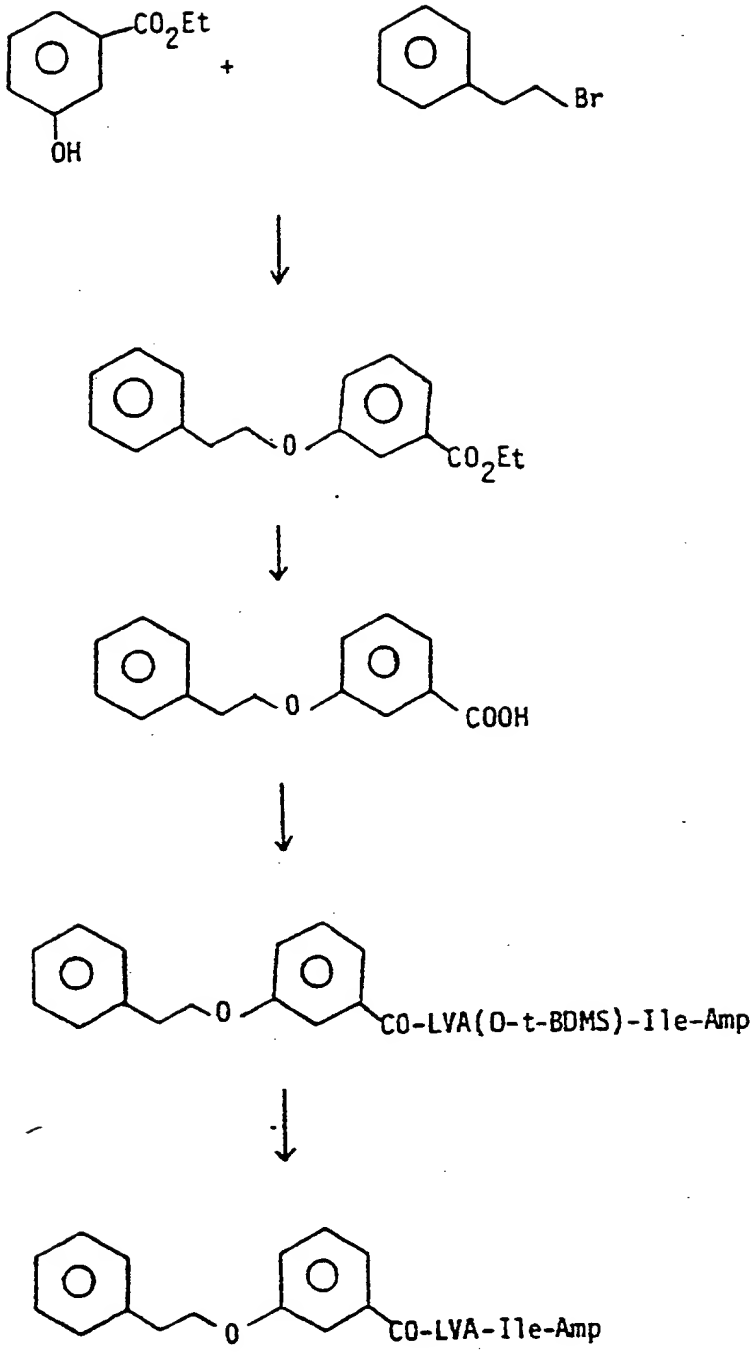

N-1
N-2
CO2Et
OH
Br
O
CO2Et
N-3
O
COOH
N-4
O
CO-LVA(O-t-BDMS)-Ile-Amp
N-5
O
CO-LVA-Ile-Amp
N-6

CHART O

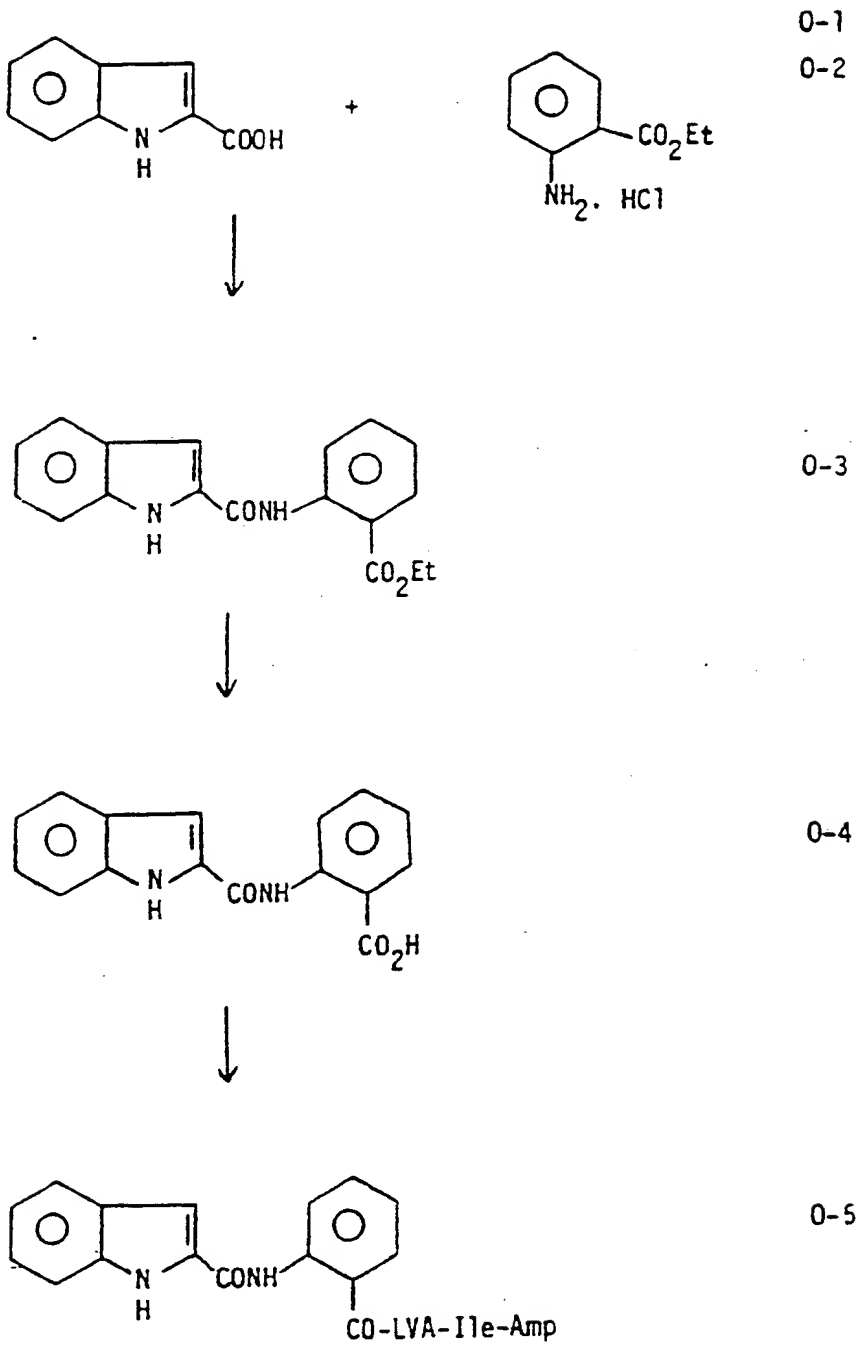

O-1
O-2
COOH
N
H
+
CO_2Et
NH_2. HCl
O-3
CONH
CO_2Et
O-4
CO_2H
O-5
CO-LVA-Ile-Amp

CHART P

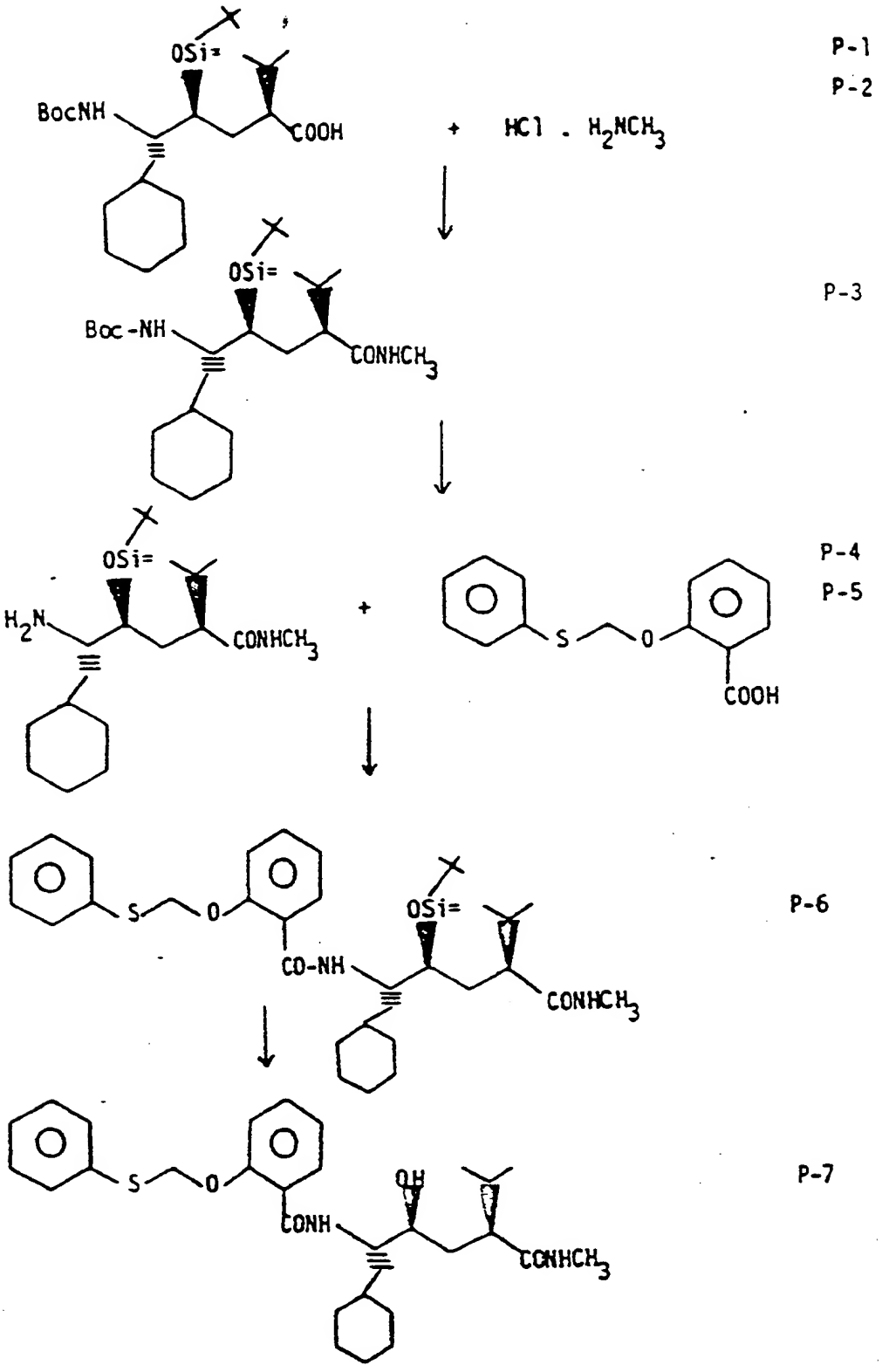
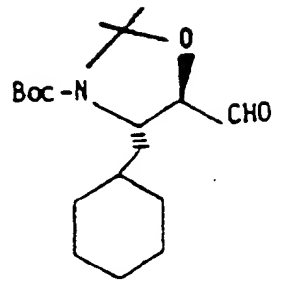
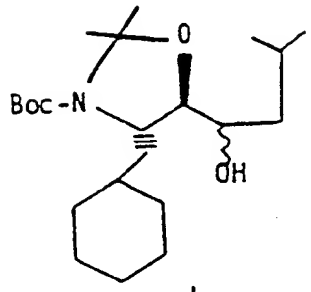

OSi=
BocNH
COOH
+ HCl . H_2NCH_3
P-1
P-2
Boc-NH
CONHCH$_3$
P-3
H_2N
P-4
P-5
S
O
COOH
CO-NH
P-6
OH
CONH
P-7

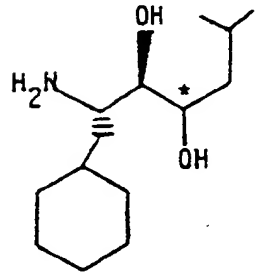
CHART Q



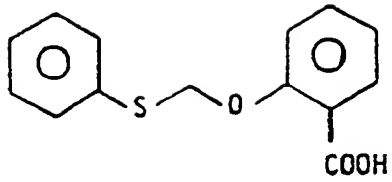
Q-1



Q-2

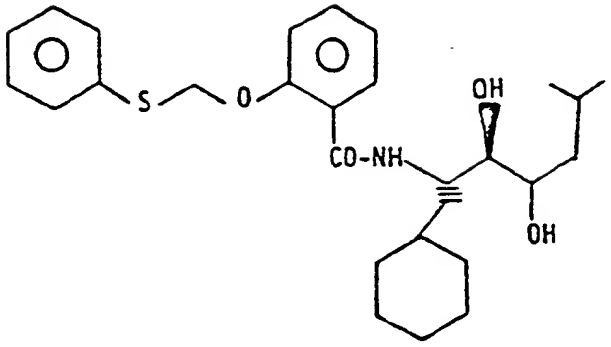


+



Q-3

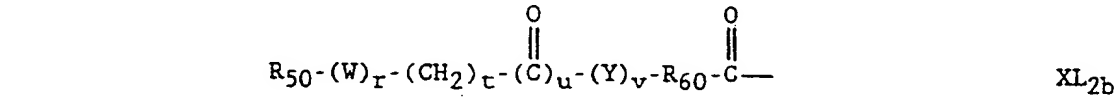
Q-4



Q-5

CLAIMS

1. A renin inhibitory peptide having a non-cleavable transition state insert corresponding to the 10,11-position of a renin substrate (angiotensinogen) and having a moiety of the formula XL_{2b}



$$R_{50}\text{-}(W)_r\text{-}(CH_2)_t\text{-}(C)_u\text{-}(Y)_v\text{-}R_{60}\text{-}C(=O)- \qquad XL_{2b}$$

in place of amino acid residues normally found at the 8,9-position of the renin substrate;

wherein R_{50} is

(a) aryl,

(b) -Het,

(c) $(C_3\text{-}C_7)$cycloalkyl,

(d) $R_{51}NHCH(R_{52})(CO)$-, or

(e) $R_{51}CH(R_{52})NH(CO)$-;

provided that R_{50} is the substituent in (d) only when r, t, and u are all zero;

provided that R_{50} is the substituent in (e) only when r, t, u and v are all zero;

wherein R_{51} is

(a) hydrogen,

(b) $C_1\text{-}C_5$ alkyl,

(c) $R_5\text{-}O\text{-}CH_2\text{-}C(O)$-,

(d) $R_5\text{-}CH_2\text{-}O\text{-}C(O)$-,

(e) $R_5\text{-}O\text{-}C(O)$,

(f) $R_5\text{-}(CH_2)_n\text{-}C(O)$-,

(g) $R_4N(R_4)\text{-}(CH_2)_n\text{-}C(O)$-,

(h) $R_5\text{-}SO_2\text{-}(CH_2)_q\text{-}C(O)$-,

(i) $R_5\text{-}SO_2\text{-}(CH_2)_q\text{-}O\text{-}C(O)$-, or

(j) $R_6\text{-}(CH_2)_i\text{-}C(O)$-;

wherein R_{52} is

(a) aryl,

(b) $-(C_1\text{-}C_4)$alkylaryl,

(c) $-(C_2\text{-}C_4)$alkenylaryl,

(d) $-(C_1\text{-}C_4)$alkyl-$(C_5\text{-}C_7)$cycloalkyl,

(e) -S-aryl,

(f) -S-(C_5-C_7)cycloalkyl, or

(g) -Het;

wherein R_{60} is

(a) aryl, or

(b) -Het;

provided that R_{60} is substituted at the ortho or meta position;

wherein W is

(a) -S-,

(b) -O-, or

(c) -NH-;

wherein i is zero to five, inclusive;

wherein for each occurrence n is independently an integer of zero to five, inclusive:

wherein p is zero to two, inclusive;

wherein q is one to five, inclusive;

wherein Y is

(a) -S-,

(b) -O-, or

(c) -NH-;

wherein r is zero or 1;

wherein t is zero to 3 inclusive;

wherein u is zero or 1;

wherein v is zero or 1;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

(a) C_1-C_3 alkyl,

(b) hydroxy,

(c) C_1-C_3 alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3 alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_{26}$,

(j) $CONHR_{26}$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3 alkylthio,

(n) C_1-C_3 alkylsulfinyl,

(o) C_1-C_3 alkylsulfonyl,

(p) -N(R_4)-C_1-C_3 alkylsulfonyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN, or

(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6 alkyl,

(ii) hydroxy,

(iii) trifluoromethyl,

(iv) C_1-C_4 alkoxy,

(v) halo,

(vi) aryl,

(vii) aryl C_1-C_4 alkyl-,

(viii) amino,

(ix) mono- or di-(C_1-C_4 alkyl)amino, and

(x) C_1-C_5 alkanoyl,

(xi) -COOH, and

(xii) $-COOR_{26}$;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen,

(b) C_1-C_5 alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7 cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_5 is

(a) C_1-C_6 alkyl,

(b) C_3-C_7 cycloalkyl,

(c) aryl,

(d) -Het, or

(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is

(a) hydrogen,

(b) C_1-C_5 alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7 cycloalkyl, or

(f) 1- or 2-adamantyl;

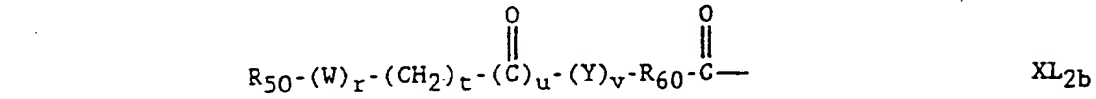
wherein R_{26} is

(a) hydrogen,

(b) C_1-C_3 alkyl, or

(c) phenyl-C_1-C_3 alkyl.

2. In a renin inhibitory peptide having a non-cleavable transition state insert corresponding to the 10,11-position of a renin substrate (angiotensinogen), the improvement which comprises inclusion in the renin inhibitory peptide of a moiety of the formula XL_{2b}



XL_{2b}

in place of amino acid residues normally found at the 8,9-position of the renin substrate;

wherein R_{50} is

(a) aryl,

(b) -Het,

(c) (C_3-C_7) cycloalkyl,

(d) $R_{51}NHCH(R_{52})(CO)$-, or

(e) $R_{51}CH(R_{52})NH(CO)$-;

provided that R_{50} is the substituent in (d) only when r, t, and u are all zero;

provided that R_{50} is the substituent in (e) only when r, t, u and v are all zero;

wherein R_{51} is

(a) hydrogen,

(b) C_1-C_5 alkyl,

(c) R_5-O-CH_2-C(O)-,

(d) R_5-CH_2-O-C(O)-,

(e) R_5-O-C(O),

(f) R_5-$(CH_2)_n$-C(O)-,

(g) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(h) R_5-SO_2-$(CH_2)_q$-C(O)-,

(i) R_5-SO_2-$(CH_2)_q$-O-C(O)-, or

(j) R_6-$(CH_2)_i$-C(O)-;

wherein R_{52} is

(a) aryl,

(b) -(C_1-C_4)alkylaryl,

(c) -(C_2-C_4)alkenylaryl,

(d) -(C_1-C_4)alkyl-(C_5-C_7)cycloalkyl,

(e) -S-aryl,

(f) -S-(C_5-C_7)cycloalkyl, or

(g) -Het;

wherein R_{60} is

(a) aryl, or

(b) -Het;

provided that R_{60} is substituted at the ortho or meta position;

wherein W is

(a) -S-,

(b) -O-, or

(c) -NH-;

wherein Y is

(a) -S-,

(b) -O-, or

(c) -NH-;

wherein i is zero to five, inclusive;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein q is one to five, inclusive;

wherein r is zero or 1;

wherein t is zero to 3 inclusive;

wherein u is zero or 1;

wherein v is zero or 1;

wherein aryl is phenyl or naphthyl substituted by zero to three of the following:

(a) C_1-C_3 alkyl,

(b) hydroxy,

(c) C_1-C_3 alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3 alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_{26}$,

(j) $CONHR_{26}$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3 alkylthio,

(n) C_1-C_3 alkylsulfinyl,

(o) C_1-C_3 alkylsulfonyl,

(p) -N(R_4)-C_1-C_3 alkylsulfonyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN, or

(t) $-CH_2NH_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6 alkyl,

(ii) hydroxy,

(iii) trifluoromethyl,

(iv) C_1-C_4 alkoxy,

(v) halo,

(vi) aryl,

(vii) aryl C_1-C_4 alkyl-,

(viii) amino,

(ix) mono- or di-(C_1-C_4 alkyl)amino, and

(x) C_1-C_5 alkanoyl,

(xi) -COOH, and

(xii) $-COOR_{26}$;

wherein R_4 at each occurrence is the same or different and is

(a) hydrogen,

(b) C_1-C_5 alkyl.

(c) $-(CH_2)_p$-aryl.

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7 cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_5 is

(a) C_1-C_6 alkyl,

(b) C_3-C_7 cycloalkyl,

(c) aryl,

(d) -Het, or

(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is

(a) hydrogen,

(b) C_1-C_5 alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7 cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_{26} is

(a) hydrogen,

(b) C_1-C_3 alkyl, or

(c) phenyl-C_1-C_3 alkyl.

3. The renin inhibitory peptide of claim 1 wherein the moiety of the formula XL_{2b} is at the N-terminus of the peptide.

4. The renin inhibitory peptide of claim 2 wherein the moiety of the formula XL_{2b} is at the N-terminus of the peptide.

5. The renin inhibitory peptide of claim 1 of the formula I

$$X\text{-}A_6\text{-}B_7\text{-}C_8\text{-}D_9\text{-}E_{10}\text{-}F_{11}\text{-}G_{12}\text{-}H_{13}\text{-}I_{14}\text{-}Z \qquad I$$

wherein X is

(a) absent,

(b) hydrogen,

(c) C_1-C_5 alkyl,

(d) R_5-O-CH_2-C(O)-,

(e) R_5-CH_2-O-C(O)-,

(f) R_5-O-C(O)-,

(g) R_5-$(CH_2)_n$-C(O)-.

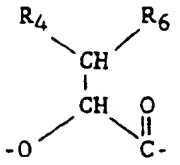
(h) $R_4N(R_4)\text{-}(CH_2)_n\text{-}C(O)$,

(i) $R_5\text{-}SO_2\text{-}(CH_2)_q\text{-}C(O)$-,

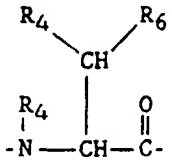
(j) $R_5\text{-}SO_2\text{-}(CH_2)_q\text{-}O\text{-}C(O)$-, or

(k) $R_6\text{-}(CH_2)_i\text{-}C(O)$-;

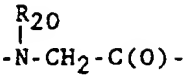
wherein A_6 is absent or a divalent moiety of the formula XL_1, XL_2, or XL_{2a};



XL_1

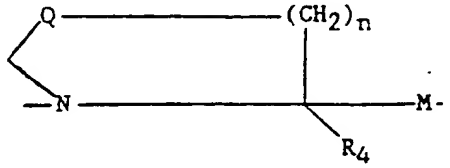


XL_2



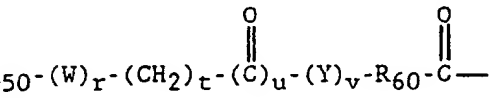
XL_{2a}

wherein B_7 is absent or a divalent moiety of the formula XL_b;



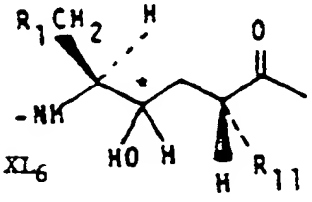
XL_b

wherein $C_8\text{-}D_9$ is the moiety of the formula XL_{2b};

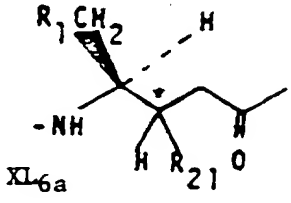


XL_{2b}

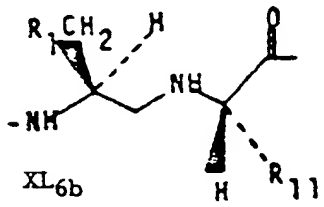
wherein $E_{10}\text{-}F_{11}$ is a divalent moiety of the formula XL_6, XL_{6a}, XL_{6b}, XL_{6c}, XL_{6d}, XL_{6e}, XL_{6f}, XL_{6g}, or XL_{6h};



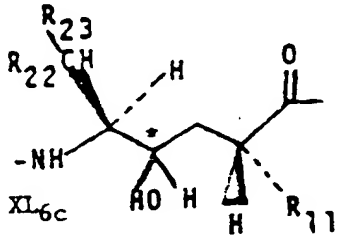
XL_6



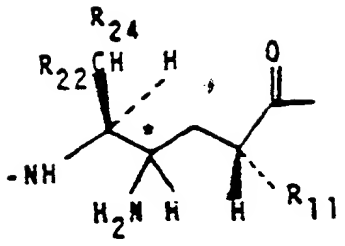
XL_{6a}



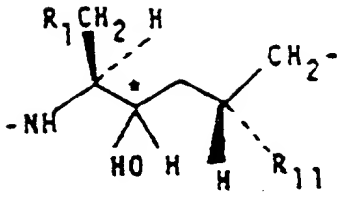
XL_{6b}



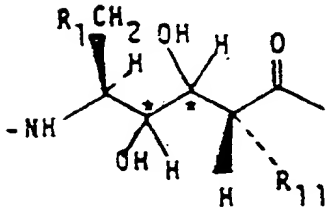
XL_{6c}



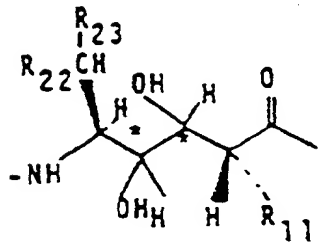
XL_{6d}



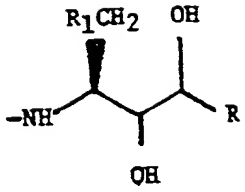
XL_{6e}



XL_{6f}



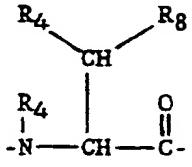
XL_{6g}



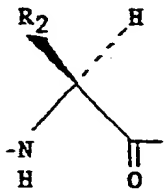
XL_{6h}

wherein * indicates an asymmetric center which is either in the R or S configuration;

wherein G_{12} is absent or a divalent moiety of the formula XL_4, or XL_{4a};

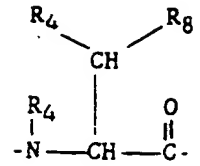


XL_4



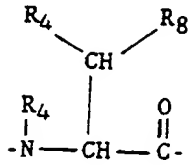
XL_{4a}

wher in H_{13} is absent or a divalent moiety of the formula XL_4;



XL_4

wherein I_{14} is absent or a divalent moiety of the formula XL_5;



XL_5

wherein Z is

(a) absent,

(b) $-O-R_{10}$,

(c) $-N(R_4)R_{14}$, or

(d) C_4-C_8 cyclic amino;

wherein R is

(a) isopropyl,

(b) isobutyl,

(c) phenylmethyl, or

(d) C_3-C_7 cycloalkyl;

wherein R_1 is

(a) hydrogen,

(b) C_1-C_5 alkyl,

(c) aryl,

(d) C_3-C_7 cycloalkyl,

(e) -Het,

(f) C_1-C_3 alkoxy, or

(g) C_1-C_3 alkylthio;

wherein R_2 is

(a) hydrogen, or

(b) $-CH(R_3)R_4$;

wherein R_3 is

(a) hydrogen,

(b) hydroxy,
(c) C_1-C_5 alkyl,
(d) C_3-C_7 cycloalkyl,
(e) aryl,
(f) -Het,
(g) C_1-C_3 alkoxy, or
(h) C_1-C_3 alkylthio;

wherein R_4 at each occurrence is the same or different and is
(a) hydrogen,
(b) C_1-C_5 alkyl,
(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7 cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_5 is
(a) C_1-C_6 alkyl,
(b) C_3-C_7 cycloalkyl,
(c) aryl,
(d) -Het, or
(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is
(a) hydrogen,
(b) C_1-C_5 alkyl,
(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-Het,
(e) $-(CH_2)_p$-C_3-C_7 cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_7 is
(a) hydrogen,
(b) C_1-C_5 alkyl,
(c) hydroxy,
(d) amino C_1-C_4 alkyl-,
(e) guanidinyl C_1-C_3 alkyl-,
(f) aryl,
(g) -Het,
(h) methylthio,
(i) $-(CH_2)_p$-C_3-C_7 cycloalkyl, or
(j) amino;

wherein R_8 is

(a) hydrogen,

(b) C_1-C_5 alkyl,

(c) hydroxy,

(d) aryl,

(e) -Het,

(f) guanidinyl C_1-C_3 alkyl-, or

(g) -$(CH_2)_p$-C_3-C_7 cycloalkyl;

wherein R_9 is

(a) hydrogen,

(b) hydroxy,

(c) amino C_1-C_4 alkyl-, or

(d) guanidinyl C_1-C_3 alkyl-;

wherein R_{10} is

(a) hydrogen,

(b) C_1-C_5 alkyl,

(c) -$(CH_2)_n R_{16}$,

(d) -$(CH_2)_n R_{17}$,

(e) C_3-C_7 cycloalkyl,

(f) a pharmaceutically acceptable cation,

(g) -$CH(R_{25})$-CH_2-R_{15}, or

(h) -CH_2-$CH(R_{12})$-R_{15};

wherein R_{11} is -R or -R_2;

wherein R_{12} is -$(CH_2)_n$-R_{13};

wherein R_{13} is

(a) aryl,

(b) amino,

(c) mono-, di or tri-C_1-C_3 alkylamino,

(d) -Het,

(e) C_1-C_5 alkyl,

(f) C_3-C_7 cycloalkyl,

(g) C_2-C_5 alkenyl,

(h) C_3-C_7 cycloalkenyl,

(i) hydroxy,

(j) C_1-C_3 alkoxy,

(k) C_1-C_3 alkanoyloxy,

(l) mercapto

(m) C_1-C_3 alkylthio,

(n) -COOH,

(o) -CO-O-C_1-C_6 alkyl,

(p) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(q) -CO-N$R_{22}R_{26}$;

(r) C_4-C_7cyclic amino,

(s) C_4-C_7cycloalkylamino,

(t) guanidyl,

(u) cyano,

(v) N-cyanoguanidyl,

(w) cyanoamino,

(x) (hydroxy C_2-C_4alkyl)amino, or

(y) di-(hydroxyC_2-C_4alkyl)amino;

wherein R_{14} is

(a) hydrogen,

(b) C_1-C_{10}alkyl,

(c) -$(CH_2)_n$-R_{18},

(d) -$(CH_2)_n$-R_{19},

(e) -CH(R_{25})-CH_2-R_{15},

(f) -CH_2-CH(R_{12})-R_{15},

(g) (hydroxy C_1-C_8alkyl), or

(h) (C_1-C_3alkoxy)C_1-C_8alkyl;

wherein R_{15} is

(a) hydroxy,

(b) C_3-C_7cycloalkyl,

(c) aryl,

(d) amino,

(e) mono-, di-, or tri- C_1-C_3alkylamino,

(f) mono- or di-(hydroxy C_2-C_4alkyl)amino,

(g) -Het,

(h) C_1-C_3alkoxy-,

(i) C_1-C_3alkanoyloxy-,

(j) mercapto,

(k) C_1-C_3alkylthio-,

(l) C_1-C_5alkyl,

(m) C_4-C_7cyclic amino,

(n) C_4-C_7cycloalkylamino,

(o) C_1-C_5alkenyloxy,

(p) C_3-C_7cycloalkenyl;

wherein R_{16} is

(a) aryl,

(b) amino,

(c) mono- or di- (C_1-C_3alkyl)amino,

(d) hydroxy,

(e) C_3-C_7cycloalkyl,

(f) C_4-C_7cyclic amino. or

(g) C_1-C_3alkanoyloxy;

wherein R_{17} is

(a) -Het,

(b) C_1-C_5alkenyl,

(c) C_3-C_7cycloalkenyl,

(d) C_1-C_3alkoxy,

(e) mercapto,

(f) C_1-C_3alkylthio,

(g) -COOH,

(h) -CO-O-C_1-C_6alkyl,

(i) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(j) -CO-$NR_{22}R_{26}$,

(k) tri-C_1-C_3alkylamino,

(l) guanidyl,

(m) cyano,

(n) N-cyanoguanidyl,

(o) (hydroxy C_2-C_4alkyl)amino,

(p) di-(hydroxy C_2-C_4alkyl)amino, or

(q) cyanoamino;

wherein R_{18} is

(a) amino,

(b) mono-, or di- (C_1-C_3alkyl)amino,

(c) C_4-C_7cyclic amino; or

(d) C_4-C_7cycloalkylamino;

wherein R_{19} is

(a) aryl,

(b) -Het,

(c) tri-C_1-C_3alkylamino,

(d) C_3-C_7cycloalkyl,

(e) C_1-C_5alkenyl,

(f) C_3-C_7cycloalkenyl,

(g) hydroxy,

(h) C_1-C_3alkoxy,

(i) C_1-C_3alkanoyloxy,

(j) mercapto,

(k) C_1-C_3alkylthio,

(l) -COOH,

(m) -CO-O-C_1-C_6alkyl,

(n) -CO-O-CH_2-(C_1-C_3alkyl)-N(C_1-C_3alkyl)$_2$,

(o) -CO-N$R_{22}R_{26}$,

(p) guanidyl,

(q) cyano,

(r) N-cyanoguanidyl,

(s) cyanoamino,

(t) (hydroxy C_2-C_4alkyl)amino,

(u) di-(hydroxy C_2-C_4alkyl)amino, or

(v) -SO_3H;

wherein R_{20} is

(a) hydrogen,

(b) C_1-C_5alkyl, or

(c) aryl-C_1-C_5alkyl;

wherein R_{21} is

(a) -NH_2, or

(b) -OH;

wherein R_{22} is

(a) hydrogen, or

(b) C_1-C_3alkyl;

wherein R_{23} is

(a) -$(CH_2)_n$-OH,

(b) -$(CH_2)_n$-NH_2,

(c) aryl, or

(d) C_1-C_3alkyl;

wherein R_{24} is

(a) -R_1,

(b) -$(CH_2)_n$-OH, or

(c) -$(CH_2)_n$-NH_2;

wherein R_{25} is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein R_{26} is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein R_{50} is

(a) aryl,

(b) -Het,

(c) (C_3-C_7)cycloalkyl,

(d) $R_{51}NHCH(R_{52})(CO)$-, or

(e) $R_{51}CH(R_{52})NH(CO)$-;

provided that R_{50} is the substituent in (d) only when r, t, and u are all zero;

provided that R_{50} is the substituent in (e) only when r, t, u and v are all zero;

wherein R_{51} is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) R_5-O-CH_2-C(O)-,

(d) R_5-CH_2-O-C(O)-,

(e) R_5-O-C(O),

(f) R_5-$(CH_2)_n$-C(O)-,

(g) $R_4N(R_4)$-$(CH_2)_n$-C(O)-,

(h) R_5-SO_2-$(CH_2)_q$-C(O)-,

(i) R_5-SO_2-$(CH_2)_q$-O-C(O)-, or

(j) R_6-$(CH_2)_i$-C(O)-;

wherein R_{52} is

(a) aryl,

(b) -(C_1-C_4)alkylaryl,

(c) -(C_2-C_4)alkenylaryl,

(d) -(C_1-C_4)alkyl-(C_5-C_7)cycloalkyl,

(e) -S-aryl,

(f) -S-(C_5-C_7)cycloalkyl, or

(g) -Het;

wherein R_{60} is

(a) aryl, or

(b) -Het;

provided that R_{60} is substituted at the ortho or meta position;

wherein W is

(a) -S-,

(b) -O-, or

(c) -NH-;

wherein Y is

(a) -S-,

(b) -O-, or

(c) -NH-;

wherein r is zero or 1;

wherein t is zero to 3 inclusive;

wherein u is zero or 1;

wherein v is zero or 1;

wherein i is zero to five, inclusive;

wherein m is one or two;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein q is one to five, inclusive;

wherein Q is

(a) $-CH_2-$,

(b) -CH(OH)-,

(c) -O-, or

(d) -S-; and

wherein M is

(a) -CO-, or

(b) $-CH_2-$;

wherein aryl is phenyl or naphthyl substituted by zero to three of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_{26}$,

(j) $CONHR_{26}$,

(k) nitro,
(l) mercapto,
(m) C_1-C_3alkylthio,
(n) C_1-C_3alkylsulfinyl,
(o) C_1-C_3alkylsulfonyl,
(p) -N(R_4)-C_1-C_3alkylsulfonyl,
(q) SO_3H,
(r) SO_2NH_2,
(s) -CN, or
(t) -CH_2NH_2;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

(i) C_1-C_6alkyl,
(ii) hydroxy,
(iii) trifluoromethyl,
(iv) C_1-C_4alkoxy,
(v) halo,
(vi) aryl,
(vii) aryl C_1-C_4alkyl-,
(viii) amino,
(ix) mono- or di-(C_1-C_4alkyl)amino, and
(x) C_1-C_5alkanoyl,
(xi) -COOH, and
(xii) -$COOR_{26}$;

with the overall provisos that:

(1) R_{18} or R_{19} is hydroxy, mercapto, or amino, or a mono-substituted nitrogen containing group bonded through the nitrogen only when n is not one;

(2) R_{12} is -$(CH_2)_n$-R_{13} and n is zero and both R_{13} and R_{15} are oxygen-, nitrogen-, or sulfur-containing substituents bonded through the hetero atom, only when the hetero atom is not also bonded to hydrogen;

(3) R_{17} or R_{19} is -COOH only when n for that moiety is other than zero;

(4) R_{16} or R_{17} is an amino-containing substituent, hydroxy, mercapto, or -Het bonded through the hetero atom only when n for that substituent is an integer from two to five, inclusive;

(5) when R_{12} is $-(CH_2)_n-R_{13}$ and n is zero, then R_{13} and R_{15} cannot both be -COOH;

(6) R_{17} or R_{19} is -Het, only when -Het is other than cyclic amino; and

(7) X is absent only when A_6 and B_7 are absent and when C_8-D_9 is the moiety of the formula XL_{2b}: and

(8) Z is absent only when E_{10}-F_{11} is the moiety of the formula XL_{6h};

or a carboxy-, amino-, or other reactive group-protected form thereof;

or a pharmaceutically acceptable acid addition salt thereof.

6. The renin inhibitory peptide of claim 5 wherein C_8-D_9 is the moiety of formula XL_{2b}.

7. The renin inhibitory peptide of claim 6
wherein R_{50} is aryl or Het;
wherein R_{60} is aryl or Het;
wherein W is -S- or -O-;
wherein Y is -O-;
wherein r is zero or 1;
wherein t is 1 or 2;
wherein u is zero;
wherein v is zero or 1.

8. The renin inhibitory peptide of claim 7
wherein X is absent;
wherein A_6 is absent;
wherein B_7 is absent;
wherein E_{10}-F_{11} is Leuψ[CH(OH)CH_2]Val;
wherein G_{12} is Ile or absent;
wherein H_{13} is absent;
wherein I_{14} is absent;
wherein Z is 2-(aminomethyl)pyridine or -N(H)(C_1-C_5alkyl);
provided that when G_{12} is absent, Z is -N(H)(C_1-C_5alkyl).

9. The renin inhibitory peptide of claim 7
wherein X is absent;
wherein A_6 is absent;
wherein B_7 is absent;
wherein E_{10}-F_{11} is XL_6 or XL_{6h};
wherein G_{12} is absent;
wherein H_{13} is absent;
wherein I_{14} is absent;
wherein Z is $-N(H)(CH_3)$ or absent;
wherein R_1 is cyclohexyl;
wherein R_{11} is isopropyl;
provided that when E_{10}-F_{11} is XL_{6h}, Z is absent.

10. The renin inhibitory peptide of claim 6
wherein R_{50} is aryl;
wherein R_{60} is aryl;
wherein W is -O- or -S-;
wherein Y is -NH-;
wherein r is 1;
wherein t is 1 or 2;
wherein u is 1;
wherein v is 1.

11. The renin inhibitory peptide of claim 10
wherein X is absent;
wherein A_6 is absent;
wherein B_7 is absent;
wherein E_{10}-F_{11} is Leuψ[CH(OH)CH_2]Val;
wherein G_{12} is Ile;
wherein H_{13} is absent;
wherein I_{14} is absent;
wherein Z is 2-(aminomethyl)pyridine.

12. The renin inhibitory peptide of claim 6
wherein R_{50} is $R_{51}NHCH(R_{52})(CO)$-;
wherein R_{51} is $(C_1$-$C_4)$alkyl-O-(CO)-;
wherein R_{52} is phenylmethyl;

wherein R_{60} is aryl or Het;
wherein Y is -NH-;
wherein r is zero;
wherein t is zero;
wherein u is zero;
wherein v is 1.

13. The renin inhibitory peptide of claim 12
wherein X is absent;
wherein A_6 is absent;
wherein B_7 is absent;
wherein E_{10}-F_{11} is Leuψ[CH(OH)CH_2]Val;
wherein G_{12} is Ile;
wherein H_{13} is absent;
wherein I_{14} is absent;
wherein Z is 2-(aminomethyl)pyridine.

14. The renin inhibitory peptide of claim 6
wherein R_{50} is $R_{51}CH(R_{52})NH(CO)$-;
wherein R_{51} is (C_1-C_4)alkyl-O-(CO)-;
wherein R_{52} is phenylmethyl;
wherein R_{60} is aryl or Het;
wherein r is zero;
wherein t is zero;
wherein u is zero;
wherein v is zero.

15. The renin inhibitory peptide of claim 14
wherein X is absent;
wherein A_6 is absent;
wherein B_7 is absent;
wherein E_{10}-F_{11} is Leuψ[CH(OH)CH_2]Val;
wherein G_{12} is Ile;
wherein H_{13} is absent;
wherein I_{14} is absent;
wherein Z is 2-(aminomethyl)pyridine.

16. The renin inhibitory peptide of claim 6

wherein R_{50} is aryl or Het;
wherein R_{60} is aryl;
wherein Y is -NH-;
wherein r is zero;
wherein t is zero;
wherein u is one;
wherein v is one.

17. The renin inhibitory peptide of claim 16 wherein R_{50} is indolyl, quinolyl or naphthyl.

18. The renin inhibitory peptide of claim 17
wherein X is absent;
wherein A_6 is absent;
wherein B_7 is absent;
wherein E_{10}-F_{11} is Leuψ[CH(OH)CH_2]Val;
wherein G_{12} is Ile;
wherein H_{13} is absent;
wherein I_{14} is absent;
wherein Z is 2-(aminomethyl)pyridine.

19. A compound of claim 5 selected from the group consisting of:
m-(Phenylthiomethyl)benzoyl-LVA-Ile-Amp;
m-(Phenylthiomethyleneoxy)benzoyl-LVA-Ile-Amp;
m-(Phenethyloxy)benzoyl-LVA-Ile-Amp;
2-(Phenoxyacetamido)benzoyl-LVA-Ile-Amp;
3-(Boc-Phe-amido)benzoyl-LVA-Ile-Amp;
2-(Phenylthioethylcarboxamido)benzoyl-LVA-Ile-Amp;
3-(Phenylthioethylcarboxamido)benzoyl-LVA-Ile-Amp;
2-(Boc-Phe-amido)benzoyl-LVA-Ile-Amp;
2-(Boc-Phe-amido)nicotinoyl-LVA-Ile-Amp;
2-(Phenylthiomethyleneoxy)benzoyl-LVA-Ile-Amp;
2-(Phenylthiomethyleneoxy)benzoyl-LVA-2S-methylbutylamide;
2-(Phenylthiomethyleneoxy)benzoyl-LVA-methylamide;
2-(Phenylthiomethyleneoxy)benzoyl-LVA-n-butylamide;
3-(Phenylthiomethyleneoxy)picolinoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-L-isoleucyl-2-(amidomethyl)pyridine;
2-(Phenoxyethyleneoxy)benzoyl-5S-amino-4S-hydroxy-2S-isopropyl-7-

methyloctanoyl-L-isoleucyl-2-(amidomethyl)pyridine;

2-(Phenylthiomethylenoxy)benzoyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexylhexanoyl-methylamide;

2-(Phenylthiomethyleneoxy)benzoyl-2S-amino-1-cyclohexyl-3R,4-dihydroxy-6-methylheptane;

3-[(1'R-tert-Butoxycarbonyl)phenethylaminocarbonyl]picolinoyl-LVA-Ile-Amp and/or 2-[(1'R-tert-Butoxycarbonyl)phenethylaminocarbonyl]nicotinoyl-LVA-Ile-Amp; and

4-[(1'R-tert-Butoxycarbonyl)phenethylaminocarbonyl]nicotinoyl-LVA-Ile-Amp and/or 3-[(1'R-tert-Butoxycarbonyl)phenethylaminocarbonyl]isonicotinoyl-LVA-Ile-Amp.

20. A compound selected from the group consisting of:

m-(Phenylthiomethyleneoxy)benzoic acid, ethyl ester;

Ethyl 2-(Phenoxyacetamido)benzoate;

Boc-Phe-3-(carbethoxy)benzamide;

Ethyl 2-(Boc-Phe-amido)benzoate;

Boc-Phe-3-(carboxy)benzamide;

2-(Boc-Phe-amido)benzoic acid;

Ethyl 2-(Phenylthioethylcarboxamido)benzoate;

Ethyl 3-(Phenylthioethylcarboxamido)benzoate;

2-(Phenylthioethylcarboxamido)benzoic acid;

3-(Phenylthioethylcarboxamido)benzoic acid;

2-(Boc-Phe-amido)nicotinic acid, ethyl ester;

2-(Boc-Phe-amido)nicotinic acid;

Methyl 3-(phenylthiomethyleneoxy)picolinate;

3-(Phenylthiomethyleneoxy)picolinic acid;

Ethyl 2-(phenoxyethyleneoxy)benzoate;

N^{α}-(4-Carboxy)nicotinoyl-D-phenylalanine tert-butyl ester and/or N^{α}-(3-Carboxy)isonicotinoyl-D-phenylalanine tert-butyl ester;

N^{α}-(3-Carboxy)picolinoyl-D-phenylalanine tert-butyl ester and/or N^{α}-2-Carboxynicotinoyl-D-phenylalanine tert-butyl ester;

m-(Phenethyloxy)benzoic acid, ethyl ester; and

m-(Phenethyloxy)benzoic acid.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US88/02255

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 K 5/02, C 07 K 7/02, A 61 K 37/64

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System [8]	Classification Symbols
IPC[4]	C 07 C; C 07 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [9]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A2, 0 161 588 (MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG) 21 November 1985 see claims	1-5
X	EP, A2, 0 173 481 (THE UPJOHN COMPANY) 5 Mars 1986 see claims	1-6
X	EP, A2, 0 206 090 (MERCK & CO. INC.) 30 December 1986 see claims	1-4
X	EP, A2, 0 220 665 (MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG) 6 May 1987 see claims.	1-6
P,X	EP, A2, 0 236 734 (CIBA-GEIGY AG) 16 September 1987 see claims	1-6

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13th October 1988	01 DEC 1988
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [XX] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND incompletely searchable

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ....., because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claim numbers 1-6, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no ~~meaningful~~ international search can be carried out, ~~specifically~~:

complete

The formulation of claims 1-6 is so complicated because of the numerous disclaimers and/or the distinct combinations of the meanings of the variable parts that it does not comply with article 6 PCT prescribing that the claims shall be clear and concise.

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 8802255 SA 23464

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 01/09/88
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0161588	21-11-85	DE-A- 3418491	21-11-85
		JP-A- 61017546	25-01-86
		US-A- 4666888	19-05-87
		US-A- 4746649	24-05-88
EP-A- 0173481	05-03-86	JP-A- 61063641	01-04-86
EP-A- 0206090	30-12-86	JP-A- 61293957	24-12-86
		US-A- 4665055	12-05-87
EP-A- 0220665	06-05-87	DE-A- 3538749	07-05-87
		JP-A- 62111956	22-05-87
EP-A- 0236734	16-09-87	JP-A- 62252757	04-11-87